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LECTURES

ON

THE COMPARATIVE PATHOLOGY OF INFLAMMATION.

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LECTURES

ON THE

COMPARATIVE PATHOLOGY OF INFLAMMATION

DELIVERED AT THE PASTEUR INSTITUTE IN 1891

BY

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Chef de Service à l'Institut Pasteur

TRANSLATED FROM THE FRENCH BY

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PREFACE.

THE outline of the natural history of inflammation here offered to the reader, is not intended as an exhaustive work on the pathology of inflammatory processes. My principal object in writing this book being to show the intimate connection that exists between pathology and biology properly so called, I have purposely omitted several points—such, for instance, as the etiology of suppuration, which has recently been so largely investigated.

As the comparative anatomy of former times treated only of man and the higher animals, so medicine has hitherto excluded all the pathological phenomena which occur in the lower animals. And yet the study of these animals, affording as they do infinitely simpler and more primitive conditions than those in man and vertebrata, really furnishes the key to the comprehension of the complex pathological phenomena which are of special interest in medical science.

If we examine the processes of inflammation from this point of view, we shall be able to form a more complete and definite idea of their real significance. In the following treatise, this theoretical side is indeed the only one considered; but here again, as in so many

other cases, the extension of theoretical knowledge must inevitably react upon its practical application.

The subject of phagocytes is frequently referred to during the course of this study on the biological theory of inflammation. I must however warn the reader that he will not find a full exposition of the phagocyte theory in this work. Many points in connection with this question come under the headings of immunity, regeneration and atrophy—points which I hope to treat separately later on.

With the exception of some slight modifications, these lectures are published in the form in which they were delivered at the Pasteur Institute, in April and May of 1891. I must, however, mention that in dealing with the destruction of the tubercle bacillus in the organism (Lecture X.), I have made use of the reactive phenomena presented by the tuberculous cells of Meriones instead of describing those in Spermophilus, as I did in my course. Rather than repeat here what has already been published in a separate paper, I have preferred to introduce an example which has not yet appeared in print.

In conclusion, I must express my great indebtedness to Professor H. de Lacaze-Duthiers, who has supplied me with valuable material for the study of inflammation in the lower animals, and also to my colleagues at the Pasteur Institute, Professor Duclaux and Dr. E. Roux, who have spared themselves no trouble in helping me in the preparation of this work.

ELIAS METCHNIKOFF.

Paris, January 15, 1892.

PREFACE TO THE ENGLISH EDITION.

I WAS much gratified when the proposal was made to me of publishing an English edition of this study on inflammation, the more so as in it I have endeavoured to apply to pathology the principles of evolution which we owe to the genius of English philosophers. I have indeed dared to put forward a new theory of inflammation, only because I felt that I had Darwin's great conception as a solid foundation to build upon, supported as it is by the doctrine of natural selection. The biological theory of inflammation has already endured the test of time. It was first advanced in several papers, the earlier of which were published about ten years ago and have been the subject of manifold attacks and criticisms. The appearance of the French edition of this work, about a year ago, was the signal for a renewal of the objections to the theory, especially by German workers. These criticisms I have endeavoured to meet in an article printed as appendix to this volume, and have shown that all the objections which have been brought forward bear only on points of subsidiary importance, without touching the root of the question, and indeed in many cases rest on simple misunderstandings which have arisen through the inadequacy of my treatment.

In replying to my critics, I have not mentioned some objections which have been raised by English pathologists. The most important feature in these is the idea that it is principally the eosinophile cells which emigrate through the vessel-wall in inflammation; that is to say, a variety of leucocytes which never acts as phagocytes. I have already replied to this statement in a special article (*Annales de l'Institut Pasteur*, No. 1, 1893), and need not repeat all my arguments here. I would only observe that the leucocytes which escape from the vessel in inflammation consist for the greater part of true phagocytes. Special investigations, which my pupils and I have carried out in my laboratory on the eosinophile cells, have shown conclusively that under no circumstances have the eosinophile granules the microbicidal action which has been attributed to them by some pathologists. These granules rather represent reserve materials, exactly similar to yolk granules and aleurone grains, which are also eosinophile.

I would conclude by expressing the hope that the history of the evolution of inflammation which is here put forward may be found to withstand the test of any further criticisms that may be directed against it; and I trust that the book in its present version may be as favourably received as has been the pleasant fate of the original.

ELIAS METCHNIKOFF.

Paris, April 10th, 1893.

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THE COMPARATIVE PATHOLOGY OF INFLAMMATION.

LECTURE I.

Infection a struggle between two organisms—Instance of the Sphærophrya—Comparative Pathology a branch of Zoology—Elementary principles of this science—Inflammation—General survey of the principal theories in relation to this phenomenon—Present views on the subject—Necessity of adopting the comparative method in the study of inflammation.

In deciding to give a few lectures on a subject belonging to the domains of pathology, I have resolved to do so solely in my capacity of zoologist. The complexity of the most important pathological processes, as studied according to the universal custom on vertebrates, is so great, even in so low a member as the frog, that it becomes impossible to analyse them or to attain any adequate conception of their real significance.

It is unnecessary to cite any special proof in support of the doctrine that disease and pathological processes are evolved in the same way as man and the higher animals themselves. In all organisms, starting from the simplest forms of life, we find infectious diseases produced by different classes of parasites. It is therefore only natural to suppose that this parasitism gives rise

to a definite series of disturbances in the infected organism, and likewise provokes phenomena of reaction in the latter.

If we examine the organisation of an animal or a plant, we find that their most characteristic features are their organs of attack and defence. The carapace of the crayfish, the shell of molluscs and the teeth of the vertebrates, as well as many other organs, are so many means of protection to these animals in their perpetual warfare. The mere enumeration of all the organs acquired for the purpose of helping them in this struggle would involve a complete account of the comparative anatomy of animals.

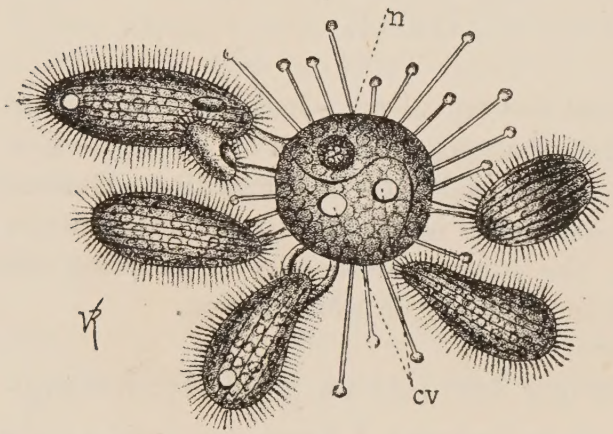

Fig. 1.—*Sphærophrya magna* (after Maupas).

Now from active aggression to infection, there is but a short step. To take an instance from the lower animals, we have only to consider the biological relations between some kinds of Infusoria. Among these minute animals there is a group of suckers, which put out their feelers in all directions, with the object of attacking other varieties of Infusoria and of absorbing their contents. (Fig. 1.) Most of these Acinetæ are Infusoria attached to different objects which occur in water, and are entirely predatory in their habits. Observation of their behaviour will explain many points in their organisation, and will also throw light on the mode of resistance offered by the infusoria they attack.

Among these Acinetæ there are some which may be distinguished by their excessive minuteness, as well as by the fact that, instead of being attached to some object and drawing their prey towards them, they are free and fasten themselves on to other infusoria larger than themselves. These minute Acinetæ pierce the outer covering of the Infusoria they attack, and take up their abode in the protoplasm of their host where they lead a parasitic existence. (Fig. 2.)

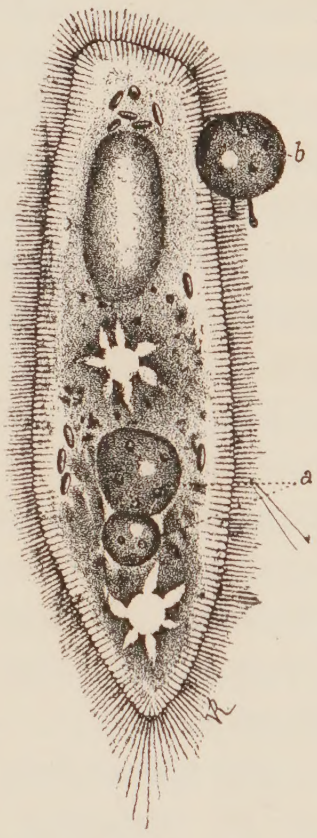

Fig. 2.—*Sphærophrya paramæciorum.*

a. Two parasitic sphærophryæ.

b. A parasite adherent to the surface of the host.

We see then that organisms which are very nearly related to each other—in fact two members of the same class (*Sphærophrya magna* and *Sphærophrya paramæciorum*)—may act as voracious aggressors or as parasites with the power of producing a definite infection. Since zoological research takes cognisance of the phenomena of attack and defence, it should likewise include the processes of infection and resistance, which are really in such close connection with the former. The phenomena of the active struggle among animals, however, being much more prominent, have attracted the attention of naturalists for years, whereas those of infection, which are far less on the surface, have been but rarely and insufficiently studied.

A branch of zoology should be devoted to the investigation of the various powers of adaptation by

means of which an animal may penetrate and remain in the body of other animals, as well as to the special study of the reactive phenomena and mechanisms which serve organisms in their resistance to parasitic invasion. A branch of zoology—the comparative pathology of animals—may thus be formed, which would differ from the present comparative pathology in many ways. Whereas the latter, which has been mainly founded on veterinary science, is only concerned with the higher animals and chiefly with mammals, genuine comparative pathology should include the whole animal world, and be treated from the widest biological standpoint.

The groundwork of such a comparative pathology was laid about five-and-thirty years ago. About this time, in 1857 and 1858, the theory of natural selection was built up on scientific foundations by Darwin and Wallace, the biological theory of fermentation by Pasteur, and the theory of cellular pathology by Virchow.

The first of these theories, which now forms the basis of all biological research, proved the genealogical evolution of organized beings, and explained the adaptation of means to an end observed in them. It demonstrated that only the characteristics which are advantageous to the organism survive in the struggle for existence, while those that are harmful to the individual are readily eliminated by natural selection.

The biological doctrine of fermentation, established by Pasteur with the discovery of the lactic ferment in 1857 and with that of the butyric ferment in 1861, showed at once in what direction the causes of infection should be sought, so that the forgotten discovery of the

anthrax bacillus was readily brought to light again by Davaine, and became the starting point of pathological bacteriology.

When Virchow demonstrated the important part played by the cells of the organism in pathological processes, a third link was formed in this chain of biological theories, which are indispensable to the founding of a true comparative pathology.

But although the groundwork of this science was laid more than thirty years ago, we are not yet in a position to treat questions of general pathology from a comparative standpoint. An inquiry into the pathological doctrines which are at present held concerning the most important morbid processes, will readily prove the truth of this statement.

As an example we will take inflammation, which is universally admitted to be the most important phenomenon in pathology. We will first examine the results obtained by the usual methods of investigation, and then we will proceed to inquire whether it would not be more desirable to treat the question of inflammation according to the comparative method.

As it is impossible to give a complete account of all the theories on the subject of inflammation, we will briefly consider those which are the most generally accepted and taught by pathologists.

For a considerable time it was principally the appearance of inflammation—the 'rubor'—which attracted the attention of medical men, who were thus frequently induced to regard hyperæmia as the most essential act in inflammation, and even to identify these two conditions. The theories concerning inflammation were thus reduced to an analysis of the hyperæmia,

which was supposed to be caused either by paralysis of the vasomotor nerves (paralytic theory) or by a spasmodic contraction of the affected arteries, accompanied by an afflux of the blood to the neighbouring parts (spasmodic theory).

But it was soon seen that hyperæmia of itself is incapable of producing true inflammation. A temporary hyperæmia, or even one of longer duration, may occur without resulting in exsudation, which is an essential condition in cases of typical inflammation. In order to explain the 'tumor,' it was suggested that the tissues at the seat of lesion had an attractive influence on the blood. This view was more definitely formulated in Virchow's conception of an increased nutritive and reproductive activity of the cells at the seat of inflammation, which gave rise to the formation of a large quantity of exsudation cells at the expense of the cells of the damaged tissues. According to this theory, hyperæmia would be merely a subordinate and entirely secondary phenomenon.

The definite proof given by Cohnheim, that the cells in inflammatory exsudations arise from the white corpuscles of the blood, first enabled pathologists to decide accurately upon one of the principal questions in connection with inflammation. After having established this undoubted fact, Cohnheim adopted the opinion of Samuel, according to whom the main factor in all inflammatory states consists in a lesion of the vessels which are attacked by the irritating cause. The inflamed vessels, being more permeable, allow the fluid and corpuscular elements of the blood to flow through them in a purely passive manner. These exsuded products collect at the part where they meet with least resistance, and thus produce the inflammatory tumour.

In this theory the tissues at the point of lesion, as well as the hyperæmia and the vasomotor phenomena, play a very unimportant part. Although certain ideas in connection with this theory have met with more or less serious objections, it is accepted, especially in Germany, by the majority of contemporary pathologists who have formulated any general conception of inflammatory processes. Some authorities adopt it in general terms, while laying stress at the same time upon the importance of the phenomena occurring in the damaged tissues and the vasomotor system. As it is not possible to bring these conditions into connection with one another, they content themselves with a simple enumeration of the changes resulting from inflammation which take place in the tissues and the vascular system.

Ziegler,[1] who is the author of the best known work on pathological anatomy at the present time, admits in his chapter "On the Definition of Inflammation," that he is unable to give a clear definition of this condition. In his own words: "The idea of 'inflammation' includes a whole series of phenomena, which occur partly in the circulation and partly in the tissues, and may be combined in various ways. As we are not here dealing with a simple pathological condition, it is impossible to give a short concise definition of inflammation. Even if only certain phenomena, such as those which occur in the circulation, were taken as characteristic of inflammatory processes, a definition of them would certainly fail to convey an adequate conception of inflammation." Accordingly, Ziegler merely gives a summary account of the changes produced by inflammation.

[1] "Lehrbuch der patholog. Anatomie," 6th edition, 1889, vol. i. p. 186.

Recklinghausen [1] holds that it is "at present impossible to determine the *primum movens*, the starting point of the changes; that is to say, the site of the earliest lesion." So he, also, is unable to do more than give a detailed and careful description of inflammatory phenomena.

The definition of inflammation put forward by Cornil and Ranvier [2] consists simply in an enumeration of the events in this pathological process. They define it as a "series of phenomena, observed in the tissues or organs, and analogous to those artificially produced in the same parts by the action of a physical or chemical irritant."

In order to simplify this complicated question, it was endeavoured to investigate this pathological condition in parts of the body devoid of blood-vessels, in which inflammation of the tissues only could be observed. Attention was concentrated upon the cartilages, and mesentery, and especially upon the cornea. From the changes observed in the cells of these organs, it was argued that vascular disturbances were not essential for the production of inflammatory phenomena in the tissues. These changes consist in proliferation of the local cells, and their return to "the embryonic condition."

Cohnheim, however, in his experiments on the cornea, demonstrated vascular intervention in experimental keratitis, and proved that immigration of leucocytes coming sometimes from the margin of the cornea and sometimes from the conjunctiva, took place into the

[1] "Handbuch d. allgemeinen Pathologie des Kreislaufs," 1883, p. 198.

[2] "Manuel d'histologie pathologique," 2nd edition, vol. i. p. 94.

seat of inflammation. These results showed at the same time that the attempts to eliminate vascular influence, even in the most evascular organs of the higher animals, had been quite futile.

An endeavour was then made to bring the changes produced within the cells themselves into the cycle of inflammatory phenomena, and Virchow's theory of parenchymatous inflammation was reinstated. The limits of inflammation were thus considerably extended. Brault[1] and others have gone even further, and sought to include under this term the acute degenerative phenomena of the cells.

We see, therefore, that the attention of pathologists has of late been mainly concentrated upon the part played by the vascular system and the local tissue-elements respectively. By the discovery of the phenomena of karyokinesis, which prepared the way for the solution of many problems dependent on the formation and origin of the cells, a new life has been given to the discussion as to whether the inflammatory cells originate at the expense of the white blood corpuscles, or in consequence of the proliferation of local cells. A discussion on this subject has recently been raised by Grawitz,[2] an ardent disciple of Virchow's, who maintains that a large proportion of pus-globules are formed from the cells of the connective tissue, and by Weigert,[3] a faithful pupil of Cohnheim, who upholds the main theory of this pathologist with regard to the origin of the inflammatory cells from the leucocytes

[1] "Etude sur l'Inflammation," Paris, 1888, p. 34.

[2] *Deutsch. med. Wochensch.*, 1889, No. 23.

[3] *Fortschritte der Medicin*, 1889, Nos. 15 and 16.

that have escaped through the vessel walls. The discovery of the karyokinetic phenomena enabled observers to ascertain, beyond a doubt, that very frequent division of the local tissue-cells takes place at the seat of inflammation. But whereas the partisans of Virchow's doctrine regarded this as a proof of the part played by these local elements in the formation of the inflammatory tumour, the adherents of Cohnheim's views interpreted this cell division as a simple phenomenon of reparation, serving to restore the mischief produced by the primary lesion. As this view became more completely accepted, it gave rise to a distinction of two classes of phenomena in inflammation ; first, inflammation properly so called, i.e. the lesion of the vessel walls and other disturbances brought about by the irritating cause ; secondly, reparation, consisting in the regeneration of the missing tissues and in the formation of the scar. The most advanced exponent of this classification, Roser,[1] went so far as to assert that inflammation is a true disease, due to the infection by microbes, and that the reparatory phenomena constitute its cure. According to this authority it is even impossible "to give a single definition of inflammation so long as this name is held to include the most heterogeneous phenomena, such as the disorders due to infection and the processes of recovery."

But besides this mode of interpreting inflammation, a movement has been for many years travelling in the opposite direction. Instead of separating inflammatory phenomena into two fundamentally distinct classes, they have been regarded as stages of a single process repre-

[1] "Entzündung und Heilung," Leipzig, 1886, pp. 9, 11, etc.

senting a salutary reaction against some injurious influence. According to this doctrine, not only regeneration and cicatrization but also the primary processes of inflammation, such as emigration and the alteration in the vessel walls, would be considered as reparatory acts serving to counteract the damage brought about by the irritant. This theory, which was clearly stated by L. Sachs more than fifty years ago, has found fresh supporters at different times. It was accepted by Buchner [1] in general terms and it has recently been developed by Neumann,[2] who maintains that true inflammation never occurs except where there has been a primary lesion of the tissues. The definition of inflammation which he endeavours to introduce, is as follows. "Under this name we should include the series of local phenomena which are developed as a result of primary lesions of the tissues (*læsio continui* or *necrosis*), and tend to cure them." [3]

From this review of the present state of our knowledge on the subject of inflammation, it is apparent that, in spite of all the pains taken by investigators, the methods hitherto adopted are inadequate for the study of phenomena so intricate and variable in their manifestations. It is not to be wondered that several authors, as, for instance, Thoma,[4] should have proposed to suppress the term 'inflammation' altogether.

In spite of many attempts to simplify the experimental conditions and to eliminate certain factors from this

[1] "Prophylactische Therapie der Lungentuberculose," 1882.

[2] "Ueber den Entzündungsbegriff," *Ziegler's Beiträge zur pathologischen Anatomie*, 1889, vol. v. p. 347.

[3] *Loc. cit.*, p. 363.

[4] *Berliner klinische Wochenschrift*, 1886.

complex process, we have only succeeded in the case of the elevation of temperature. By studying inflammation in cold-blooded animals incapable of generating heat to any appreciable extent, such as frogs, it is seen that true inflammation can take place in the total absence of heat, one of the four classical factors (dolor, calor, rubor, tumor). In these animals the inflammatory nature of the phenomena in question is so evident, that no one has raised any objection to the application of the term 'inflammation' in cases where the temperature is not raised and where, consequently, the word is no longer applicable in its etymological sense.

The frog has always been chosen on account of the facilities it presents for experimental study, without realizing that in so doing a method of comparative pathology was adopted. It is along these lines that investigation should proceed, but the comparison should be extended to still lower members of the animal kingdom, in order to eliminate further factors and to study these phenomena in a yet more simple condition.

As we have already seen, all attempts to obtain inflammation in the higher animals without the intervention of the vessels have failed, since it is impossible to exclude the circulatory system, even in the most isolated tissues. In order to obtain definite results, we must direct our attention to the large field presented by the invertebrata, among which there are many animals completely devoid of blood vessels. The comparative method has already rendered good service, not only in the realm of natural sciences, properly so called, but even in the study of the most complicated phenomena. Thus Psychology owes much to the observation of

psychical phenomena in the lowest animals, and even in the social sciences, such as ethnology or political economy, investigation has often been extended to the most inferior races. Pathology is almost the only science in which the comparative method has been ignored, although it has to do with phenomena which present complications from every point of view, and it would be particularly profitable to make use of such methods for enlarging the scope of its investigations.

The question may be thus formulated. Do the factors (traumatic or infective) which evoke the series of phenomena known as inflammation in man and the higher animals, produce any analogous conditions in the lower vertebrata, such as Amphioxus, or in the invertebrata? Is the existence of a circulatory system essential for the setting up of inflammation, or does this also occur in animals which possess no blood vessels, and in this case how does the nervous system act? For inflammation to take place, is it necessary that the animal should possess a certain number of differentiated organs or may it consist merely of an agglomeration of non-differentiated cells? Do we find anything analogous to inflammation in plants? Are there any instances of inflammatory action in unicellular organisms? In the following lectures we shall discuss these questions one by one, and endeavour to answer them.

LECTURE II.

Are the unicellular organisms subject to traumatic and infectious maladies ?—Merotomy of the Amœbæ and Infusoria—Lesions of Vaucheria—Epidemic disease of Amœbæ, caused by the Microsphæra—Intracellular digestion in the Protozoa—Digestion of bacteria—Epidemics in the Infusoria : disease of the nucleus and nucleolus—Division of infected Paramæcia, and the means whereby they rid themselves of the parasite—Acinetæ—Chytridia.

WE will first inquire whether the unicellular organisms, which abound in the media surrounding us, are subject to infectious diseases, and whether they are susceptible to those influences which produce in us a more or less pronounced inflammation. We shall afterwards examine the changes that these influences call forth in these lowly organisms.

In man and the higher animals a traumatic lesion, even when insignificant, invariably provokes the series of phenomena which characterize inflammation. In unicellular organisms the resulting events are much simpler. If we cut an Amœba in two, there is not even a wound formed along the line of section, for the edges unite immediately after the passage of the instrument. (Figs. 3, 4.) Two new Amœbæ are thus produced ; the one which encloses the nucleus continues to grow and behaves in all respects like a normal individual, while the other, which is without any nucleus, dies at the end

of a longer or shorter period.[1] Some other inferior organisms, which contain several nuclei, as for instance Actinophrys, can be divided into several pieces, each of which is regenerated in a very short time, provided that it still contain a fragment of nucleus.[2] In the Infusoria, which possess a more highly differentiated protoplasm, artificial bisection

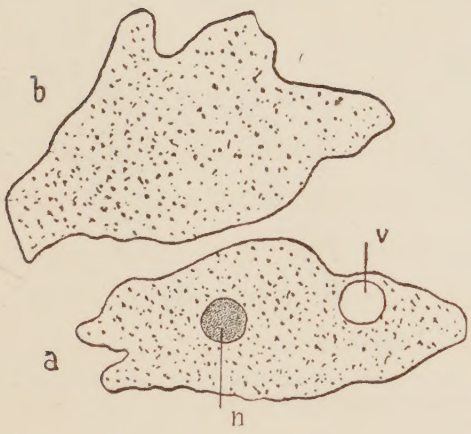

Fig. 3.—An amœba immediately after bisection.

a. The half containing the nucleus *n*.
b. Half without nucleus.
v. Contractile vesicle.

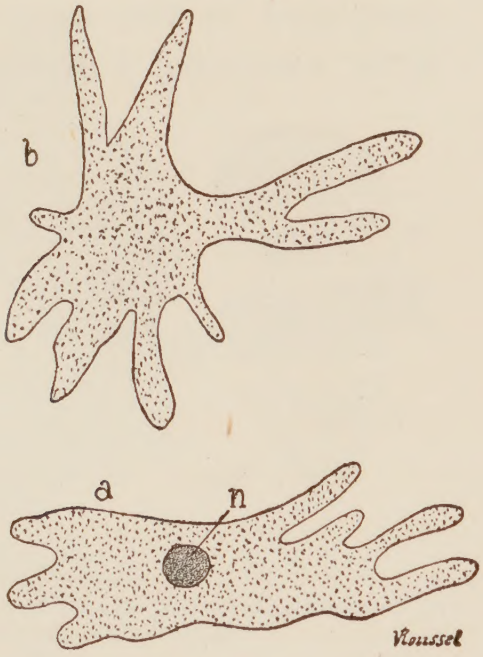

Fig. 4.—The same amœba five minutes after the operation.
(After Bruno Hofer.)

produces a wound which lays bare the inner layer of protoplasm. After a short time, however, the edges of the peripheral layer grow over the wound, and secrete a new cuticle, thus securing complete cicatrisation. (Fig 5.)

[1] Bruno Hofer. "Experimentelle Untersuchungen üb. d. Einfluss des Kerns auf das Protoplasma." *Jenaische Zeitschr. f. Naturwiss.*, 1889, vol. xxiv. p. 109, pl. iv. and v.

[2] K. Brandt. "Ueb. Actinosphærium Eichhornii," 1887, p. 30.

These phenomena are almost exactly the same whether the fragments be provided with a nucleus or not. In those with a nucleus, however, regeneration is complete in a very short time (often in less than twenty-four hours), while the others gradually atrophy and in the end always die. Balbiani,[1] who has published an important paper on the merotomy of the Infusoria, is indeed of opinion that cicatrisation is never properly completed in the fragments without a nucleus, the latter exercising a decided influence on the secretion

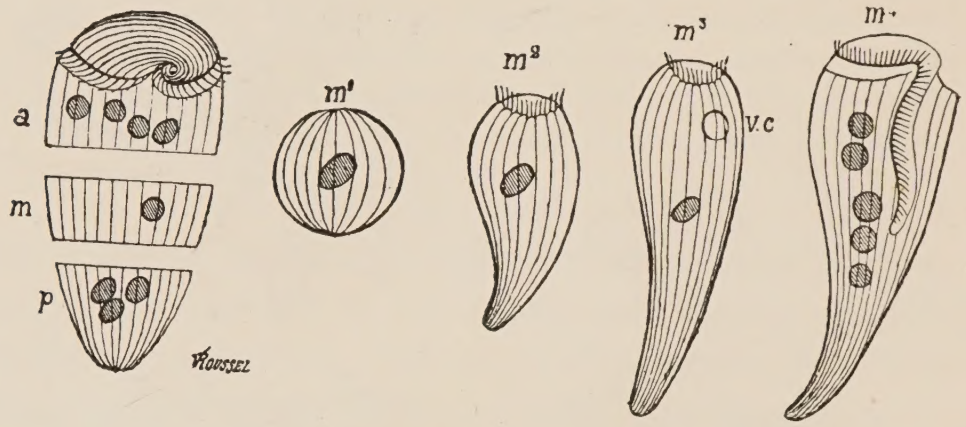

Fig. 5.—Merotomy of a *Stentor*.
a. Anterior fragmemt ; *m*, middle fragment ; *p*, posterior fragment ; m^1, m^2, m^3, m^4, stages in the regeneration of the middle fragment.
(After Balbiani.)

of the cuticle. In some species, such as *Trachelius ovum*, the wounds caused by the section are immediately covered over by the ectoplasm, and the separate fragments that still possess a nucleus are completely regenerated in less than five hours.

In the same way unicellular plants may undergo severe injuries without necessarily perishing in consequence. Thus Hanstein[2] has observed that, when a

[1] "Recherches expérimentales sur la mérotomie des infusoires ciliés." *Recueil zoologique suisse*, vol. v. 1888.

[2] *Vide* Frank, "Die Krankheiten der Pflanzen," 1880, vol. i. p. 97.

part of the unicellular alga Vaucheria is cut or crushed, it is only the damaged part that dies, while the rest of the cell is healed by the secretion of a cuticular layer on the injured surface, and the formation of a sort of sequestrum.

In these phenomena then, in the lower organisms, we have to do simply with a regeneration that takes place more or less completely and readily. But after traumatic lesions it is infection that most frequently provokes inflammation. Now, infectious diseases are very common among the Protozoa and unicellular plants. Even the lowest members of these classes are sometimes subject to infection.

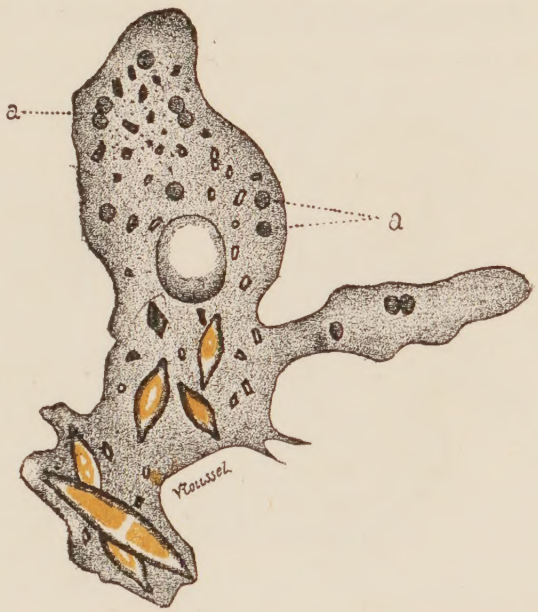

Fig. 6.—Amœba infected by the *Microsphæra*. *a*. Early stage.

Thus in the Amœbæ I have observed an epidemic caused by a very simple organism, which occurs in the form of a round cell provided with a very delicate wall and a nucleus, and capable of multiplying by division. The large Amœba with rounded pseudopodia, that feeds upon diatoms, sometimes contains by the side of these brown algæ a small number of these round cells (Fig. 6), which I shall allude to under the name of *Microsphæra*. As the general aspect of the amœba together with its protoplasmic movements remain normal, no one would suspect this rhizopod to

be diseased. Continued observation shows, however, that whereas the enclosed diatoms undergo digestive changes, the Microsphæræ divide and multiply without let or hindrance within the protoplasm of the amœba. This latter ejects the diatoms and becomes gradually less and less active, showing that it is not in a healthy condition. At the same time the protoplasm becomes filled with Microsphæræ, and the Amœba invaded by the parasite finally perishes. (Fig. 7.)

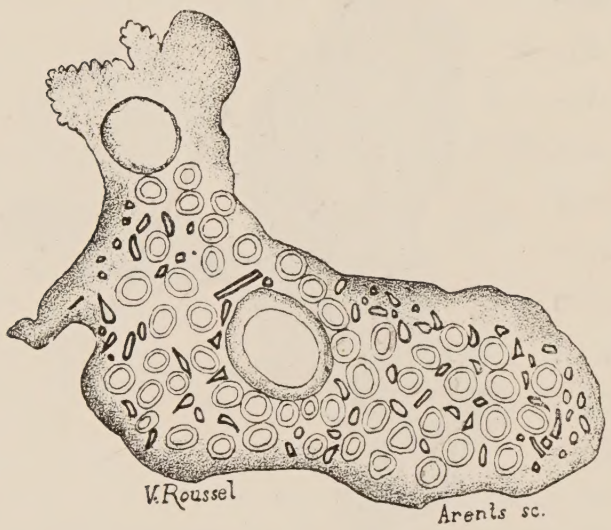

Fig 7.—A dying Amœba, full of parasitic Microsphæræ.

This case is interesting since it shows us that an organism, although composed almost entirely of a protoplasm which has the power of readily digesting the contents of diatoms, can nevertheless be infected by another organism. The infecting agent, which is to all appearance insignificant, has yet the power of resisting the digestive influence of the Amœba and of bringing about its death. To explain this fact, we must assume some property in the parasite enabling it to produce in the interior of the amœba a substance which protects the Microsphæra, and is at the same time toxic for the amœba.

Thus the infection develops in spite of the marked power of intracellular digestion possessed by the Amœbæ. A closer observation of the group of Protozoa compels us to the conviction that this

digestive function must play an important part in the mutual relations of these lowly organisms. Many Rhizopoda and Infusoria live in media swarming with other unicellular organisms, including bacteria. The latter, which multiply very rapidly, serve as food to many of the Protozoa. Thus various Amœbæ devour bacilli, which undergo certain definite changes in the interior of their protoplasm. Without altering their shape, the bacilli acquire the power of taking up solutions of vesuvine, which does not stain these microbes when living in their natural conditions. (Fig. 8.) Since

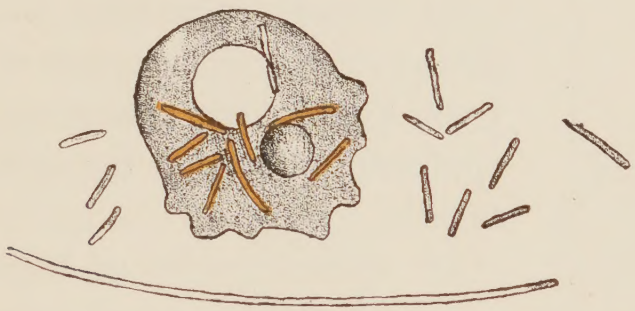

Fig. 8.—An Amœba living in the midst of bacilli of which it has taken up a certain number.

precisely similar changes are also observed in the interior of Vorticellæ and other Infusoria which live on bacteria, it is evident that they are due to a digestive influence exerted by the contents of the Protozoa. This conclusion is in harmony with the observation of B. Hofer[1] on digestion in Amœbæ. This investigator has shown that the more the food is altered in the interior of these Rhizopods the more easily does it stain with the aniline colours.

We may often see flagellated Monads taking up filaments of Leptotrix several times as long as themselves (Fig. 9), and finally enclosing them in their digestive vacuoles. (Fig. 10.) It is sometimes possible to follow

[1] *Jenaische Zeitschrift*, vol. xxiv., 1889, p. 109.

all the changes undergone by the bacteria within an infusorium, as in the case of the digestion by Stentor of the sulphobacterium Thiocystis, observed by Le Dantec.[1]

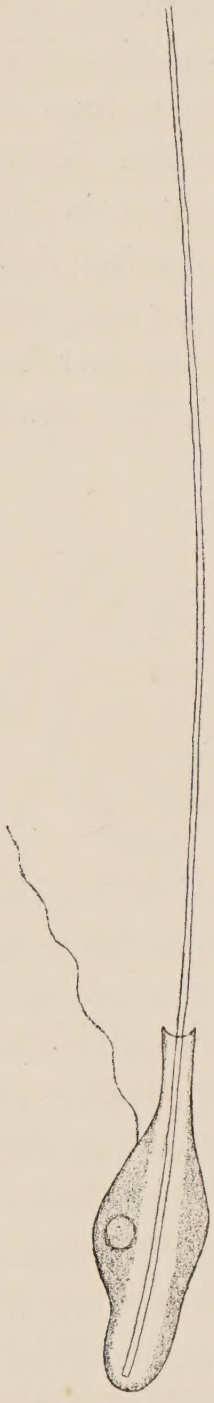

Fig 9.—A Monad in the process of englobing a filament of Leptotrix.

It is evident that the digestive function of the protoplasm of the Protozoa must hinder the invasion of these animals by the lower organisms, and it is only in certain special cases that the latter can live as parasites within the Rhizopoda and Infusoria. As I have already mentioned an infective disease of the former class of animals, I will pass to the consideration of an epidemic affecting the ciliated Infusoria.

In several species of Infusoria and especially in Paramæcia, attention has long been called to the presence in the nucleus of a number of very fine rods, which J. Müller, who first discovered them, looked upon as spermatozoids. These bodies were afterwards studied by several observers, of whom I may specially mention Balbiani and Bütschli, and were regarded by them as parasitic bacteria. In reality they are organisms quite distinct from the Bacteriaceæ, and belong to a special group, consisting of several species. Some of these develop in the nucleus, replacing its contents,

[1] "Recherches sur la digestion intracellulaire," Lille, 1891, p. 53.

while another species attacks only the nucleolus. (Fig. 11.) The parasite, in its vegetative condition, occurs in the form of elongated fusiform cells or rods which multiply by transverse division or sometimes by budding. Arrived at maturity, the parasites are transformed into peculiarly shaped spores resembling in their general appearance either bacilli or spirilla.[1]

In spite of the abundance of these microbes in organs so important as the nucleus and nucleolus, the infected Infusoria remain capable of division, when they do not die from exhaustion. In the process of division a certain number of parasites escape from the nucleus into the surrounding protoplasm, whence they are expelled just like any other indigestible body that has been swallowed by the infusorium. Hafkine has shown that, if placed in exceptionally favourable conditions, the Paramæcium may continue to divide and produce successive generations of infected infusoria; at each division however, the organism rids itself of a certain number of the parasites, so that finally they may be all expelled and a complete cure result.

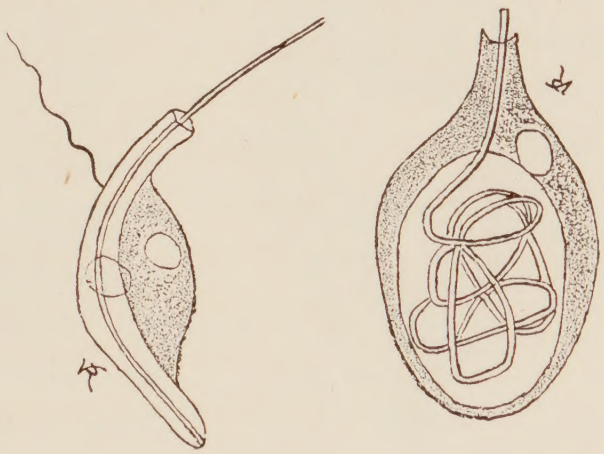

Fig. 10.—Leptotrix enclosed in the digestive vacuole of a Monad.

Hafkine has never succeeded in producing infection

[1] *Vide* the investigation of Hafkine, carried out at my instigation in my laboratory, and published in the *Annales de l'Institut Pasteur*. Vol. iv., 1890, p. 148.

by introducing Paramæcia into capillary tubes containing spores of the parasite; for the Infusorium, although it swallowed a certain number of the spores, surrounded them with a nutrient vacuole (Fig. 12, 13), and then ejected them as it would any excrementitious matter. In order that a spore should germinate, it must avoid the digestive and expulsive action of the protoplasm of the Infusorium, and penetrate into the nucleus or nucleolus, neither of which has any digestive capacity.

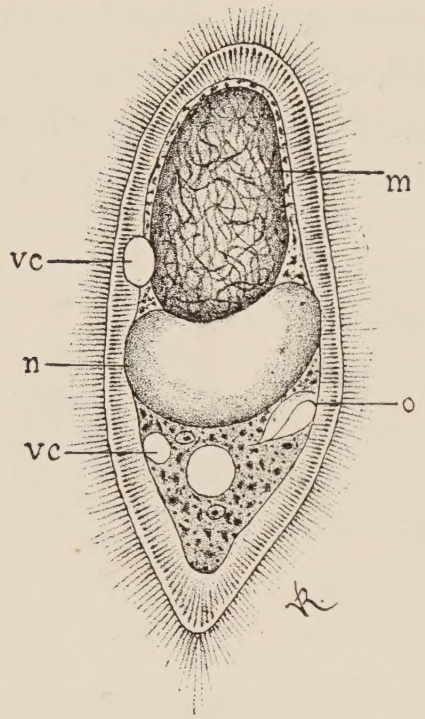

Fig. 11.—Paramæcium with its nucleolus filled with parasites.

o. mouth; *n*. nucleus; *m*. affected nucleolus; *v. c*. contractile vesicle.

We see that in this case, as in the disease of the Amœbæ, the microbe, in order to infect the Protozoon, has to combat the power possessed by its protoplasm of ejecting or digesting the parasite. The same holds good in all cases where we find the invader lodged in the digestive contents of an infusorium.

The majority of the infectious diseases of these Protozoa are doubtless caused by the parasitism of suctorial Infusoria or Acinetæ, which I have already mentioned in the first lecture. In spite of the delicacy of their cuticle, these parasites offer complete resistance to the digestive action of the protoplasm of their hosts, although in many cases the latter (as e.g. Stylonychia) are distinguished by their voracity and the ease with which they digest their prey. As already mentioned,

the young Acinetæ fix themselves on to the surface of other Infusoria, and penetrate into the endoplasm of the latter by means of their active movements. Once arrived in the central mass of protoplasm, the parasites grow considerably, divide, and give rise to a number (fifty or more) of young individuals, some of which escape from the body of the infusorium to attack another, after a certain period of freedom.

In order to survive in the interior of the Infusoria, the Acinetæ must exercise some paralysing influence on the digestive function. It is probable that these parasites secrete

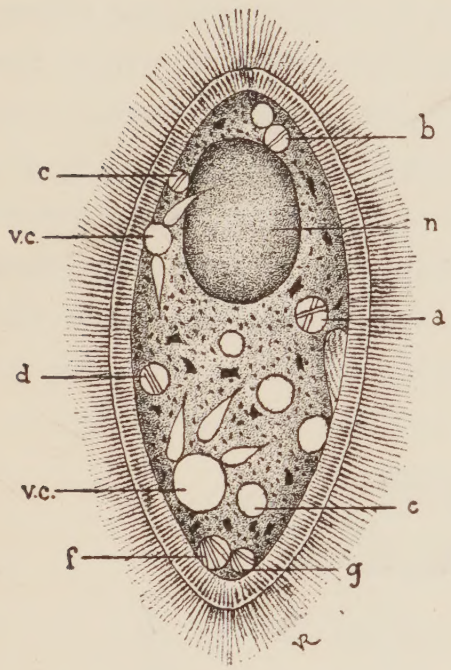

Fig. 12.—A Paramæcium which has taken up some spores of the parasite.

a. b. c. d e. f. g. spores surrounded by a vacuole; *n.* nucleus; *v. c.* contractile vesicle.

Fig. 13.—A vacuole containing spores (very highly magnified).

some toxic substance, since one often sees various Infusoria fall into a paralysed condition and die in consequence of the attacks of free Acinetæ.[1]

By their growth within the Infusoria the Acinetæ give rise to degeneration of the nucleus, which breaks up into small round granules. In many cases, however,

[1] For an account of what is known about the Acinetæ, see Bütschli, "Protozoa," in Bronn's "Classen u. Ordnungen des Thierreichs," vol. iii., 1889, pp. 1823 and 1842.

these parasites do not kill their hosts, which may even preserve their power of multiplication. Much more dangerous for the unicellular organisms are the infections produced by the fungi belonging to the group of Chytridiaceæ, which in most cases attack Infusoria incapable of intracellular digestion, such as those which obtain their nourishment simply by diffusion. They may also attack Infusoria capable of intracellular digestion, but in this case the infection occurs while the Infusorium is in an inactive or encysted condition, during which time digestion does not take place. The intracellular Chytridium, after penetrating into the interior of the Protozoon, becomes round and immobile, and absorbs the substance of its host, which dies, while the parasite gives rise to zoospores.

Fig. 14.—*Euglena viridis* enclosing a Chytridium.

We will take as an example the Chytridium which so often infects the *Euglena viridis*, and which was discovered by Klebs.[1] Among these Flagellata, which abound in stagnant water, we may find individuals which are to all appearances in perfectly good health, but enclose a round body, provided with a nucleus and a very delicate cuticle. (Fig. 14.) This foreign body grows gradually larger, and divides into a number of small cells which become converted into conical

[1] *Untersuchungen aus d. botan. Institute in Tübingen*, vol. i., 1883. See also Hafkine, *Annales des sciences naturelles: zoologie*, 1886, pp. 330, 336, &c.

zoospores. (Fig. 15.) The zoospores bore their way out of the Euglena and escape into the surrounding water. In the course of this development, the affected individual presents unmistakable signs of disease. The green chromatophores are rapidly absorbed, and the Euglena becomes highly anæmic. Its contents at the same time undergo pigmentary degeneration, evidenced by the formation of scattered brown granules which become gradually more and more numerous. When the parasite has attained the zoospore stage, the Euglena dies in consequence of the infection.

Fig. 15.—*Euglena* filled with zoospores of the Chytridium.

The encysted condition, during which the Euglena viridis is protected by a capsule, seems to preserve it from the attacks of the Chytridium, since this is only found within the mobile Euglenæ. On the other hand, the cysts of this infusorium are often invaded by the *Polyphagus Euglenæ*, which represents another genus of the Chytridiaceæ.

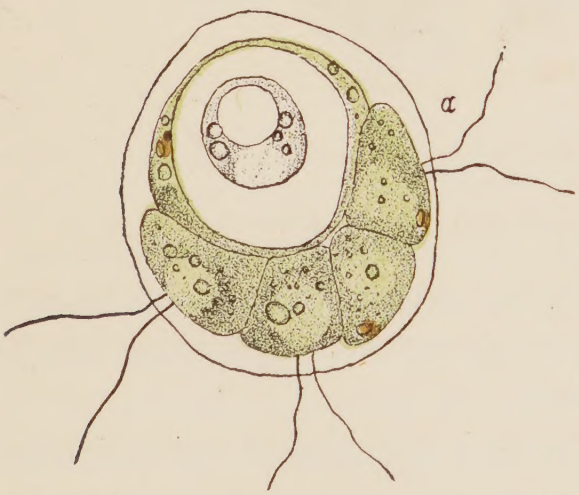

Fig. 16.—*Pandorina* with one cell attacked by an *Olpidium*.

The colony-forming Flagellata are equally subject to infection by the Chytridiaceæ. *Pandorina morum* (one of the Volvocineæ) is often attacked by an *Olpidium*. The presence of the latter in the body of the flagellated

Monad causes a secretion of fluid, which collects to form a vacuole. (Fig. 16.) The parasitic cell, which is small and transparent, increases in size at the expense of its host, and becomes filled with fatty granules interspersed with transparent vacuoles. Soon afterwards it sends out a conical process which pierces the cell-wall of the Pandorina (Figs. 17, 18), and forms an outlet by which the zoospores produced by the segmentation of the contents of the parasite escape. At

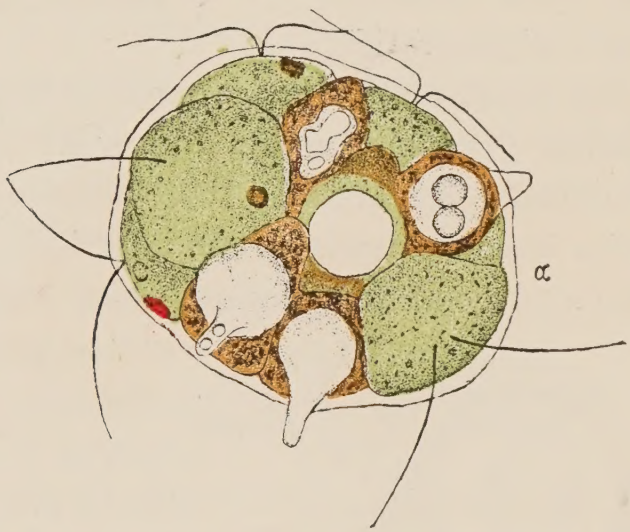

Fig. 17.—Another *Pandorina* with five infected cells.

other times the parasite, without giving rise to zoospores, may secrete a thick external membrane, and be transformed into a cyst.

As in the case of Euglena, the invaded cell undergoes pigmentary degeneration, and always ends by dying and disintegrating. The neighbouring cells of the colony however remain quite unaffected. They preserve complete mobility, show pulsation of their contractile vesicles, and divide in a perfectly normal manner. (Fig. 18.) The disease and death of one or even of the greater number of the sixteen members of

the colony has absolutely no effect on the individual cells which have escaped infection by the parasite.

This brief account of artificial lesions and of the infectious diseases of the unicellular organisms, while showing the inadequacy of our present knowledge on the subject, at the same time enables us to appreciate to some extent the general character of these phenomena. With regard to those which are called forth by the lesions, the most striking fact is the complete power of regeneration possessed by these beings. As

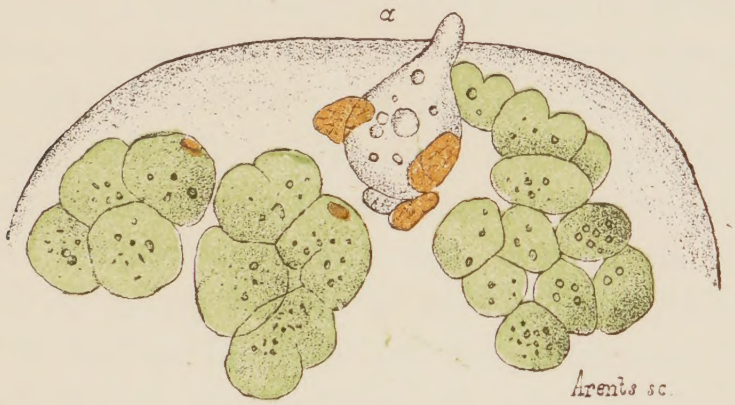

Fig. 18.—Part of an affected *Pandorina*; and the zoosporangium of the parasite *a*.

we have seen, a detached segment can regain its normal form in a very short time, some hours or even minutes after the section.

After what has been said in the first chapter, we are justified in assuming generally that the relations between the Protozoa and the micro-organisms which infect them are to be regarded in the light of a struggle between two living species. The parasites are often nothing else than voracious organisms which, in consequence of their minute size, do not attack their prey directly, but make their way into the bodies of the Protozoa which serve them for food. This carnivorous

nature of the parasites is seen not only in the Acinetæ, but also in the parasitic Flagellata which are allied to the Vampirellæ and other voracious organisms. In the cases of infection however, the struggle assumes a more complicated and indirect character. The parasite makes its onslaught by secreting toxic or solvent substances, and defends itself by paralysing the digestive and expulsive activity of its host; while the latter exercises a deleterious influence on the aggressor by digesting it and turning it out of the body, and defends itself by the secretions with which it surrounds itself.

Although these phenomena do not come under the heading of the struggle for existence in the strictly Darwinian sense (i.e. competition for the survival of the fittest among individuals of the same species), yet they are all more or less directly connected with the struggle for survival that is always going on between the representatives of the different orders of living beings. In this struggle an important part devolves on the power of intracellular digestion, which is so generally met with in the Rhizopoda and Infusoria and is not entirely wanting even in the Protozoa which obtain their food entirely by osmotic absorption.

LECTURE III.

Plasmodium of Myxomycetes—Puncture by a glass tube—Cauterisation—Chemical excitation—Trophotropism—Chemiotaxis—Habituation of the plasmodium—Negative chemiotaxis—Repulsion of the plasmodium in the presence of bacteria—Digestion of bacteria by the plasmodium—Sensibility of the plasmodium—Fixed plants having no true intracellular digestion—Necrosis and regeneration—Waldenburg's experiments—Functions of the cell-wall—De Bary's observations on *Peziza sclerotiorum*—Tumours of plants.

WE have now to consider the pathological phenomena which occur in multicellular organisms; and first of all we meet with a group which is very important for several reasons and especially interesting on account of the simple organisation of its members. I refer to the Myxomycetes—a group presenting both animal and vegetable properties and characterised by the fact that it passes through a plasmodium stage. This plasmodium is composed of the largest masses of protoplasm known to occur in nature.

The plasmodium, as is well known, represents a colossal amœboid organism formed by the fusion of a large number of zoospores of the Myxomycetes and enclosing numerous nuclei embedded in a common protoplasm. Branching in all directions, the plasmodium is able to move about on the various objects (dead leaves, wood, &c.) on which it lives; it shows amœboid movements

at the edges of its ectoplasm, while the inner layer of its protoplasm (or endoplasm) is the seat of rapid currents, recalling those of volcanic lava. The plasmodium readily encloses any solid bodies within its reach, and partially digests them by the help of a peptic ferment and an acid which it secretes around its food.[1] The residue as well as the indigestible bodies are turned out by the plasmodium, thus forming tracks which mark the places where the protoplasmic processes have been. At a certain time the plasmodium produces

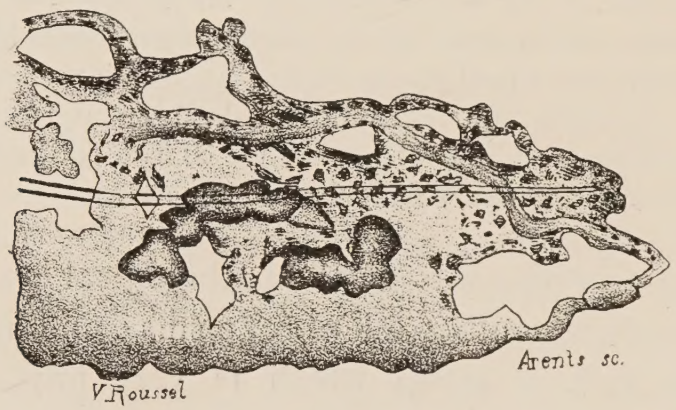

Fig. 19.—A part of the plasmodium enclosing a glass tube.

sporangia, which are usually in the form of minute fruit, and enclose a number of spores provided with a tough envelope.

On account of its great extent, which may amount to as much as a foot or more, the plasmodium offers many advantages for the study of protoplasm in general and of pathological phenomena in particular.

In order to observe the effect of a lesion upon a plasmodium, we may introduce a solid foreign body, such

[1] The peptic ferment was discovered by Krukenberg. *Untersuchungen aus dem physiol. Instit. d. Univ. Heidelberg*, vol. ii., 1878, p. 273. Concerning the acid of the plasmodia, see *Annales de l'Institut Pasteur*, 1889, p. 25.

as a minute glass tube, into the protoplasm of a Physarum. The puncture by the tube tears a part of the plasmodium, which diffuses into the surrounding fluid. But the chief mass of protoplasm is in no way affected by the tube, which it moreover englobes after a short time just as if it were a particle of food. (Fig. 19.) After retaining the tube for a longer or shorter time, the plasmodium ejects it like any other substance that it is unable to utilise as nourishment.

We may irritate the plasmodium in another way. If we take a specimen (such as the yellow plasmodium of Physarum) on an object glass and touch its central part with a minute glass rod previously heated in a flame, we shall produce thermal excitation instead of a mechanical lesion. Immediately after being touched, the central part of the plasmodium dies and may be clearly distinguished from the living peripheral portions, which remain motionless as if nothing had occurred, and are unaffected by the necrosed portion. A few hours later however the plasmodium wakes from its passive condition and creeps away from the dead part.

Fig 20.—Plasmodium cauterised by nitrate of silver.

Chemical irritants operate in a still more powerful way. If we apply a minute fragment of nitrate of silver to the edge of a plasmodium of Physarum lying on a piece of glass, and wash the injured spot directly afterwards with a one per cent. solution of sodium

chloride, (in order to precipitate any nitrate which may have become dissolved,) we shall see that the edge touched by the nitrate of silver dies and becomes detached from the rest of the plasmodium. (Fig. 20.) The latter reacts immediately by a rapid change in the direction of its movements. Before the operation, the protoplasmic currents were tending towards the edge where the nitrate was applied (this spot having been chosen for the experiment on this account); directly afterwards

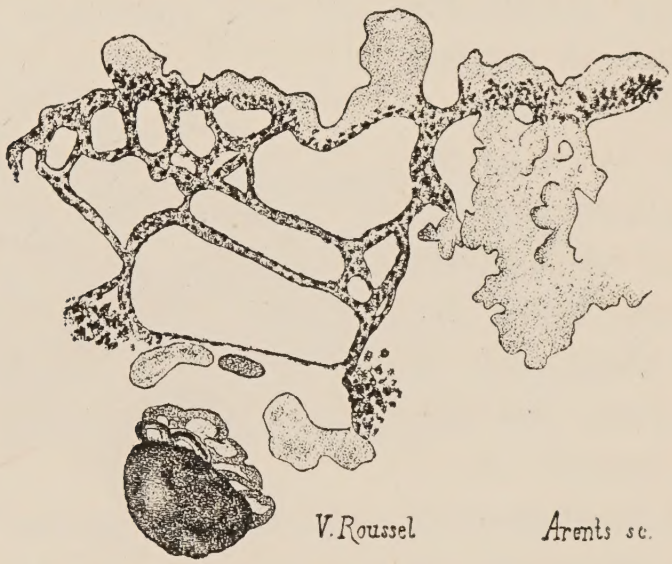

Fig. 21.—The same plasmodium 50 minutes after the stage represented in Fig. 20.

they were turned towards the sides of the plasmodium and soon assumed a direction completely opposed to the original one. (Fig 21.) At the end of an hour from the beginning of the experiment, the plasmodium had moved some distance from its first position, leaving the dead residue behind.

In both of these experiments the plasmodium forsakes the portions injured by thermal or chemical agencies. The much more rapid removal of the plasmodium in the second case may be attributed to the more powerful influence of the nitrate of silver.

We thus see that irritating agents excite in the plasmodium either a course of events similar to those which accompany the taking up of any solid nutriment, or else a more or less marked repulsion. In attempting to produce a reaction which should correspond to the condition of inflammation in the higher animals, we have brought about the phenomena of attraction or repulsion which occur so frequently in the lives of plasmodia and the inferior animals generally.

As early as 1884, Stahl [1] discovered that a decoction of dead leaves (on which so many of the Myxomycetes feed) has the property of attracting the plasmodia, whereas solutions of salt, sugar, and numerous other materials, act in a contrary manner, repelling the plasmodia to a greater or less distance. In connecting these phenomena with those of nutrition, Stahl gave them the name of *positive trophotropism* when it was a question of attraction, and of *negative trophotropism* in cases of repulsion. Pfeffer,[2] having found that the female organs of certain cryptogams (ferns, mosses, and selaginellæ) attract the spermatozoids with a different object from that of nutrition, grouped all these various forms of sensibility to chemical agents under the general heading of *chemiotaxis* (positive or negative), a term which was very soon generally adopted.

Since, as we have just shown, these phenomena of sensibility play an undoubted part in pathological processes, it is desirable to consider them in somewhat greater detail. Chemiotactic phenomena are met with not only in the Myxomycetes and the spermatozoids of

[1] *Botanische Zeitung*, 1884, Nos. 10–12.

[2] *Untersuchungen aus d. botan. Institute in Tübingen*, vol. i. p. 363.

the above-mentioned cryptogams, but also in Bacteria, Flagellata, Volvocineæ,[1] and in the zoospores of fungi, such as the Saprolegniaceæ.[2] Hence it is evident that we have here to do with a phenomenon of general import.

It cannot be denied that by means of positive chemiotaxis the organisms are directed in their search after nutrient substances, and are enabled to approach the bodies with which they have to establish relations, as in the case of the spermatozoids attracted by an ovum. By means of negative chemiotaxis, on the other hand, they can escape injurious influences. This rule, although true generally, cannot be applied to every particular case. Thus Pfeffer[3] has seen spirilla and animalcules ('bodons') dart into too highly concentrated solutions of sugar and glycerine, to which attracting substances had been added, where they inevitably perished.

The analogy between these phenomena and the sensations of man and the higher animals is obvious. One among many proofs of this analogy consists in the fact that the chemiotaxis of the lower animals is subject to the same law of Weber which has been established for the sense perceptions of man. In order that a bacterium (*B. termo*) or the spermatozoids of ferns (the organisms on which Pfeffer has made his remarkable observations) may be affected by a change in their surrounding media, it is essential that this change should attain a certain degree. Thus the Bacterium termo placed in a solution of peptone of definite strength, will not move towards a

[1] *Untersuchungen aus d. botan. Inst. in Tübingen*, vol. ii. 1888, p. 582.

[2] *Botanische Zeitung*, 1890, Nos. 7–11.

[3] *Unters. a. d. botan. Inst. in Tübingen*, vol. ii. p. 627.

more concentrated solution of peptone, until this is five times as strong as the first solution. Having ascertained these proportions, Pfeffer formulated for the chemiotaxis of these unicellular bodies the same law as for the sense perceptions of man, viz. that when the excitation is increased in geometrical proportion, the sensation is increased in arithmetical proportion, or, in other words, that the reaction varies as the logarithm of the excitation.

Now although the two orders of phenomena conform to the same law, there is quantitatively a great difference between them. Man can appreciate a difference of weight equalling one-third, of temperature amounting to one-thirtieth, of light equivalent to one-hundredth, whereas the spermatozoids of ferns are not affected by and do not react to an alteration in the chemical composition, until the quantity of the substance which is acting on them is augmented twenty-nine times. The Bacterium termo is indifferent to an increase of concentration until this amounts to four times the original concentration.[1]

In order to test the chemiotactic sensibility of the plasmodium, I placed several specimens of the plasmodium of *Didymium farinaceum* in 0·1, 0·01, 0·05, 0·005, and 0·0005 per cent. solutions of hydrochlorate of quinine. The last two solutions did not prevent the plasmodium from advancing or even from inserting several processes into them; whereas the first three solutions exercised a pronounced negative chemiotactic effect. (Plate II., figs. 3-6.) The plasmodium therefore can appreciate the difference between 0·05 and 0·005 per cent. of hydrochlorate of quinine.

The plasmodium, in common with other of the lower organisms, has the important power of growing gradually

[1] Pfeffer, *loc. cit.*, vol. ii. p. 637.

accustomed to solutions which in the beginning it avoided. Stahl was the first to notice that the plasmodium of Fuligo, which is at first repelled by a solution of sea-salt in the proportion of 2 per cent. or less, after having been deprived for some time of water finally adapts itself to the changed conditions and dips its processes into the salt-water. Here we have an instance of negative chemiotaxis which, as the result of imperceptible alterations in the protoplasm, is converted into positive chemiotaxis.

As this fact is of great importance from a general point of view, I was desirous of watching the process myself. For this purpose, I placed a plasmodium of Physarum extended on a glass slip into a vessel containing a solution of 0·5 per cent. sodium chloride. The plasmodium immediately showed negative chemiotaxis and moved away from the surface of the liquid. It was then changed to another vessel containing a 0·25 per cent. solution of the same salt. The plasmodium was at first repelled, but after the lapse of a few hours it drew near the liquid into which it then immersed the end of its processes. With the view of noting how far this power of adaptation extended, I replaced the plasmodium in the first vessel with the 0·5 per cent. salt solution. It again receded from the fluid ; but at the end of about twelve hours it approached the surface of the water, without however touching it.

By means of negative chemiotaxis, therefore, the plasmodium is enabled to avoid injurious influences ; as we have seen, it recedes from bodies which burn it, such as the nitrate of silver, and even from necrosed portions of its own organism, as in the experiment of the application of a heated object. It is probable that

the same property may serve to protect the plasmodium against the attack of other organisms, especially of pathogenic microbes.

Stahl has observed that plasmodia are never attacked by parasites. This fact he seeks to explain by referring it to the facility with which the plasmodia move about from place to place, as well as to their power of expelling foreign substances—a property which is connected with the intracellular digestion of solid bodies. Although no direct observations on the expulsion of parasitic organisms by the plasmodium have so far been made, yet it is extremely probable that this occurs, especially as Pfeffer[1] has watched the plasmodia of Chondrioderma ejecting living Pandorinæ and Diatoms. Moreover the direct observations on the expulsion of parasitic spores by the Paramæcia tend to support Stahl's deduction on this subject.

The following experiment was made with the object of ascertaining the true significance of the movements of the plasmodium. I spread out a plasmodium of Physarum on a slide, and placed it midway between two small glass vessels, one of which was filled with a stagnant infusion of dried leaves, full of bacteria, infusoria and other of the lower organisms, the other with the same infusion after filtration through several layers of filter-paper. The two ends of the plasmodium were connected with the liquid in the two vessels by strips of blotting-paper. The plasmodium soon began to approach the filtered liquid, moving along the strip which was soaked in it. Another experiment made in

[1] "Ueber Aufnahme und Ausgabe ungelöster Körper." *Abhandlungen d. math. phys. Klasse der k. sächs Gesellsch. d. Wissenschaften*, vol. xvi. 1890, p. 161.

the same way, with a few slight modifications, was attended by exactly the same result, showing that the plasmodium preferred the liquid which was free from microbes. In order to ascertain how far this preference extended, I repeated the experiment, only exchanging the filtered fluid for a fresh infusion of dead leaves in cold water, which was consequently colourless. This time the plasmodium advanced towards the stagnant infusion, in spite of the microbes which it contained.

The repulsion of the plasmodium in the presence of the lower organisms is evidently merely relative; this is in harmony with the fact that the Myxomycetes in their amœboid condition have the power of englobing microbes. Saville Kent has observed amœboid zoospores of *Physarum tussilaginis* which were filled with bacteria. Later on Lister[1] made some highly interesting researches on the inclusion of bacteria by the zoospores of different Myxomycetes. The bacteria, seized on by the pseudopodia, are dragged into the interior of the amœboid plasma and lodged in the nutritive vacuoles. Here they become less and less distinct, and appear to be almost completely dissolved. A zoospore of *Chondrioderma difforme* will completely digest a couple of large bacilli in about an hour and a half.

The powers of digestion and expulsion possessed by the plasmodium, combined with its property of negative chemiotaxis, are of real service to it in reacting against injurious excitants.

The plasmodia, in common with a considerable number of other lowly organisms, are endowed with several forms of sensibility besides that known as chemiotaxis.

[1] *Journ. of the Linnæan Soc., Botany*, vol. xxv. 1890, p. 435.

They avoid sunlight, and are powerfully attracted to the damper places, thus evincing a kind of hydrotropism. Moreover, this positive hydrotropism is converted into negative hydrotropism just before the period of fructification, when the plasmodium seeks a dryer spot (Stahl). The plasmodia are also endowed with tactile sensibility.

Fixed multicellular plants, which have no powers of locomotion or of digesting and excreting foreign bodies, react to the various injurious factors with which they may come in contact in a different manner from the plasmodia, which can either avoid dangerous objects or can eliminate them by digestive or excretory processes.

A thorn introduced into the plasmodium is dealt with like any other foreign body that becomes enclosed in the amœboid mass. As it cannot be digested, it is simply ejected altogether. If introduced into the tissue of a plant, the same thorn would produce a lesion of the cells, and the injured cells would inevitably perish. The damage is soon repaired with the help of the neighbouring cells, which rapidly multiply and form either a mass of cork or a true scar composed of several tissues.[1] In both cases there is active cellular neo-formation at the injured spot. Waldenburg,[2] who has studied these phenomena from the point of view of their analogies with inflammation in the higher animals, says: "Plants may therefore suffer from inflammation, if by this term we imply only the lesions produced by the irritant, as well as the tumour induced by these lesions,

[1] Frank, "Die Krankheiten der Pflanzen." Breslau, 1880, vol. i. p. 95, etc.

[2] *Virchow's Archiv*, vol. xxvi. 1863, pp. 145 and 322, Tab. v.

and leave out of account the blood-vessels and nerves" (p. 344). Inflammation would thus be only an irritation of the tissues (tumefaction, growth) *plus* a vascular congestion.

The phenomena of repair in plants have on more than one occasion been quoted in support of the attraction theory of inflammation, and especially in favour of Virchow's theory of a nutritive and formative hyperactivity of the inflamed tissues. But unfortunately no account has been taken of the conditions intermediate between plants and the higher animals, and consequently the most characteristic phenomena of true inflammation have been lost sight of altogether.

The new cells produced at the seat of injury in plants frequently secrete thicker and tougher cell-walls than usual. The cuticle in fact represents the true protective organ of the plant. The instance quoted in the preceding lecture of a Chytridium which only attacks the Euglena in its mobile and never in its encysted condition, may be taken as a confirmation of this statement. The walls of the vegetable cells are too resistant for many of the microbes, and especially for those which cannot penetrate actively into the tell-contents. This is probably the reason why bacterial infection so rarely takes place in plants. On the other hand, vegetable organisms are very liable to be attacked by fungi, which grow rapidly and in many cases secrete a diastase which dissolves the cellulose cuticle of the plant. The parasitic fungus, once within the cell, absorbs the contents without further hindrance. The cells that are thus invaded die, while the others that remain alive, undergo rapid proliferation which results in the overgrowth of parts, amounting in some

cases to a hypertrophy of the entire organism affected, as in the case of *Euphorbia Cyparissias* when infested by the æcidium of *Uromyces Pisi.* The presence of a parasite, whether it be a fungus or a member of the animal kingdom, often excites the formation of special tumours or galls.

As in the healing of wounds, infections[1] in plants are accompanied with regenerative phenomena, dependent on the rapid proliferation of the cells that are not directly affected. We do not however find processes analogous to the essential phenomena of inflammation in the vegetable world. For these we must pass to the consideration of the representatives of the animal kingdom.

[1] The most carefully recorded instance is undoubtedly that of the *Peziza sclerotiorum* on which De Bary (*Botanische Zeitung*, 1886) made his classical observations. This fungus germinates on the surface of the plant and sends out filaments with which it subsequently penetrates the tissues. (The *Peziza sclerotiorum* invades a large number of plants.) In order to effect an entry, the parasitic filaments secrete oxalic acid and a ferment which dissolves the cellulose. The parasite feeds on the juice of the cells which have perished under the influence of its secretions, and its mycelium grows into the interstices between the cells, rarely penetrating the latter. De Bary has observed that the Peziza easily finds its way into young plants, but is unable to force an entrance into older plants of the same species. This immunity is probably owing to the fact that the parasite cannot dissolve the cellulose of the old cells. The control experiments showed in fact that the extracted juice of the fungus was able readily to digest the walls of the young cells and was quite without effect on those of the older individuals of the same plant.

It is evident that the power of resistance possessed by the vegetable cell is specially dependent on the toughness of its cuticle. The parasite in order to infect the plant must first perforate or dissolve this membrane.

LECTURE IV.

Transition from the unicellular organisms to the Metazoa—Sketch of the phagocytella theory—Protospongia—Sponges: their organisation—their three layers—their nutrition—Intracellular digestion—Ablation of parts of the Sponge—Artificial division—Introduction of pointed bodies—Utilisation of foreign bodies to assist in forming the skeleton—Fate of the organisms which have penetrated into the interior of the Sponges—Protective function of the ectoderm—Comparison with the Myxomycetes—Comparison with the inflammation of vertebrata.

IN passing to the animal kingdom, we have to confess that we are at present ignorant of the way in which the multicellular animals or Metazoa are derived from the Protozoa. The gap between the most highly developed members of the latter class and the lower kinds of Metazoa is too wide and can only be bridged over by hypotheses based on the embryological study of different animals. Putting aside several groups of parasites which have undoubtedly lost much of their primitive character (*Dycyemides*, *Orthonectides*), we find that even the simplest forms of the Metazoa, such as the Sponges, are composed of a multiplicity of organs, arranged in three well-known layers: the ectoderm, the mesoderm and the endoderm. In order to obtain a knowledge of a more simple condition of animal life, we must turn to the embryos of Sponges and of other inferior organisms, such as the Medusæ and their allies. Here we may readily

meet with stages in which the animals are composed of two layers, one of which constitutes an enveloping membrane for the larva, the other is formed by the inner cells, grouped in a different manner. These latter cells are sometimes collected into a solid mass, a kind of parenchyma, composed of amœboid elements; or they may be arranged evenly to form an epithelial layer surrounding a digestive cavity. The question as to which of these two forms may be considered the more primitive has been much discussed. I think that the absence of a digestive cavity, the irregular shape of the cells, together with various other facts afforded by the comparison of the embryogeny of many lower animals (which do not come within the range of this pathological survey), lead to the conclusion that the parenchymatous stage is the more primitive of the two. I have called this stage by the name of *Phagocytella*,[1] on account of the power which the cells of the inner layer possess of englobing various solid bodies, and more especially for the reason that the digestive cells of the whole organism are derived from this layer. The latter in the first place produces the endoderm which lines the intestinal canal and its appendages, and secondly the whole or a part of the mesoderm which also includes a large number of digestive cells or *phagocytes*.

The phagocytella stage may readily pass into the *Gastrula* stage,[2] which has two epithelial layers, one of which represents the wall of the primitive intestine that opens by a primordial orifice or blastopore.

[1] Cf. my account of the Phagocytella theory in my "Embryologische Studien an Medusen," Wien, 1886.

[2] For an account of the Gastræa theory, see Hæckel "Gastræa-Theorie." Jena, 1874.

This gastrula is so to speak the starting-point for all the Metazoa.

The structure of the Metazoa when reduced to its simplest condition, that of the phagocytella, is somewhat analogous to that of certain colony-forming Protozoa. In these cases the colonies are made up of two kinds of individuals: the flagellated individuals

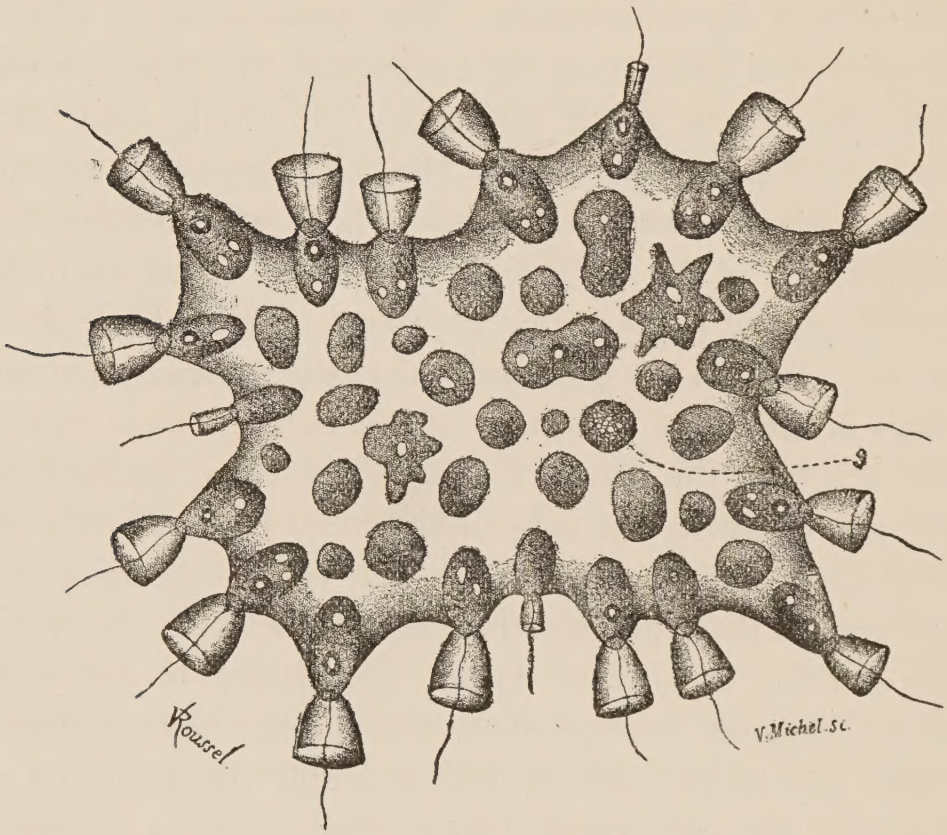

Fig. 22.—*Protospongia Hæckelii* (after Saville Kent).

forming a sort of outer layer (Fig. 22), and the amœboid individuals, situated in the inner mass of the colony. The former would thus correspond to the elements of the ectoderm, which so frequently consists of flagellated cells, and the latter would constitute a kind of inner parenchyma, composed of amœboid cells, which are at the same time phagocytic in their nature. In these colonies of infusoria, termed *Protospongia* by

their discoverer Saville Kent,[1] the two layers are not yet clearly defined, since the individuals of which they are made up pass readily from the one form into the other.

By means of these colonies on the one hand and of the organisms resembling the phagocytella on the other, we are almost in a position to bridge over the gap between the Protozoa and the Metazoa.

I should not have dwelt upon these hypotheses in these lectures on the comparative pathology of inflammation, did not their consideration afford an opportunity of studying the general significance of the presence of these amœboid cells which are able to englobe solid bodies. We have met with them in the various classes of Protozoa, and we find them again even in the most primitive forms of Metazoa. Now the co-operation of amœboid cells in inflammation as it occurs in the vertebrates is a fact of the greatest importance, which has received almost universal acceptance.

As low down in the animal scale as the most inferior Metazoa we have to do with these cells. The Sponges are of such undifferentiated organisation that they were long considered to be colonies of Protozoa, consisting, like the Protospongia, of separate flagellated and amœboid individuals. Later on it was however ascertained that they bore a certain relationship to the Polyps and their allies (Cœlenterata). It was then found that they are formed of three characteristic layers. The outer layer or ectoderm covers the whole structure with flat epithelial cells, the contours of which are very clearly defined after the application of a solution of nitrate of silver. The cells themselves are evidently

[1] "The Manual of Infusoria," 1880–1882.

contractile—a property which is more readily observed at the free edges of the young cells, where amœboid prolongations belonging to the ectodermic elements are seen. The contractility of these cells is certainly concerned in the remarkable phenomenon of the opening of the numerous pores which are scattered over the whole surface of the Sponge and are bordered by two or more flat cells. These pores open to permit of the passage of a stream of water with the minute particles which it holds in suspension. The liquid first enters a system of efferent canals which are also lined by a pavement epithelium, the origin of which is not yet known. It then passes into canals or into round cavities (the 'ciliated chambers') which are covered with a cylindrical epithelial layer, the cells of which possess a single large flagellum. These cells, which present a striking analogy to many flagellated infusoria, form part of the endoderm and represent typical phagocytes, since they attract and englobe a large number of fine granules which are carried along by the stream.

Besides these flagellated phagocytes of endodermic origin, the Sponges contain a large number of mobile cells, which are typical amœbæ and form part of the mesoderm, being situated between the ectoderm and the cylindrical epithelium. Although it has not so far been definitely ascertained how the foreign particles penetrate the mesoderm after they have reached the interior of the Sponge, yet it has been clearly shown that they are largely absorbed by the mesodermic cells themselves. If a coloured substance, such as carmine indigo or sepia, be added to the water in which the Sponges are immersed, it will be found soon afterwards that many of the grains of colouring matter have been

enclosed by the endodermic cells, as well as by the amœboid phagocytes of the mesoderm.

In certain Sponges (as for instance in several calcareous Sponges,) there are very few mesodermic cells, which consequently take but a small part in englobing foreign bodies; in others again, especially in the silicious kinds, the mesoderm is much better developed, and its more numerous cells can therefore take in a proportionately larger number of these minute particles. There are a few species, such as the *Siphonochalina coriacea*, whose mesodermic cells alone enclose all foreign bodies, so that the cylindrical cells of the endoderm merely serve to keep up the continuous passage of the fluid through the Sponge. The phagocytes of both layers have the power of rejecting insoluble matters, which collect in the larger efferent canals and are expelled from the organism through large apertures of crater-like shape, the walls of which, according to some authors, are furnished with muscular fibres.

We are however chiefly concerned here with the fact that the mesodermic phagocytes are able to digest the substances as well as to englobe them, and to reject the insoluble residue. Many years ago Lieberkühn[1] observed the digestion of Infusoria which had found their way into the mass of amœboid cells of soft-water Sponges, and pointed out the analogy of this phenomenon with the digestion of Infusoria by the Rhizopoda or other Protozoa. This has been confirmed by other investigators. Thus I have seen[2] Oxytricha, Glaucomæ, and Actinophrys dissolved in the midst of

[1] *Müller's Archiv für Anat. und Phys.*, 1857, p. 385.

[2] *Zeitschr. f. wissench. Zoologie*, vol. xxxii. 1879, p. 371.

a mass of the mesodermic phagocytes of a young Spongilla, and afterwards the foreign bodies which had been swallowed by these Protozoa englobed by the same phagocytes. The Euglenæ, when sucked into the Spongillæ by the current, become likewise surrounded by the mesodermic phagocytes ; but whereas their protoplasm is then digested, the grains of chlorophyll and paramylum remain intact for an indefinite time.

Fig. 23.—A mesodermic phagocyte of a young Spongilla surrounded by several ectodermic cells.

The mesodermic cells of young Spongillæ, immediately after their escape from the gemmules, can enclose foreign bodies even before the endoderm is developed. The young Sponge at this stage consists only of a layer of flat ectodermic cells and an irregular mass of mesodermic cells, a certain number of which soon begin to secrete spicules. If carmine grains be placed in the

water inhabited by the Spongillæ, they find their way in without apparently injuring the wall, and are at once englobed by the amœboid phagocytes of the mesoderm. (Fig. 23.)

The above facts are so invariable in their occurrence and may be so readily observed, that it is very extraordinary that de Lendenfeld,[1] in his monograph on the physiology of Sponges, should seek to throw doubt on the matter. This author asserts that carmine, when added to the water which filters through the Sponges, is very rarely deposited in the amœboid cells and then only where there is some lesion of the outer layer of cells, and that in a normal Sponge it is only the cylindrical cells of the endoderm which will seize on the carmine. De Lendenfeld lays stress on these conclusions, in spite of the fact, which he acknowledges, that the fat-globules of milk are readily absorbed by the mesodermic phagocytes. This is a sufficient proof of the part taken by these cells in the intracellular digestion of Sponges. Moreover his memoir contains direct indications of the presence of carmine grains in the amœboid cells of the mesoderm. Thus this author describes that he has seen numerous carmine grains in the phagocytes of *Chondrosia reniformis*, the species on which he has bestowed the most study. Further, he has even found them in these cells two hours and a half after the introduction of the carmine into the water, at a period when the cylindrical elements of the chambers no longer contained any granules.

Since these facts remove all doubts that the amœ-

[1] "Experimentelle Untersuchungen über die Physiologie der Spongien," *Zeitschr. f. wissensch. Zoologie*, vol. xlviii. 1889, p. 406.

boid cells of the mesoderm of the Spongillæ have the power of taking in and digesting foreign particles, I have endeavoured to ascertain the conditions which might influence this function. Following up the knowledge we have acquired concerning the typical intracellular digestion in the Protozoa and the Myxomycetes, which secrete around the object they have englobed an amount of acid sufficient to convert the colour of litmus from blue to red, I placed a few grains of blue litmus into the water containing some young

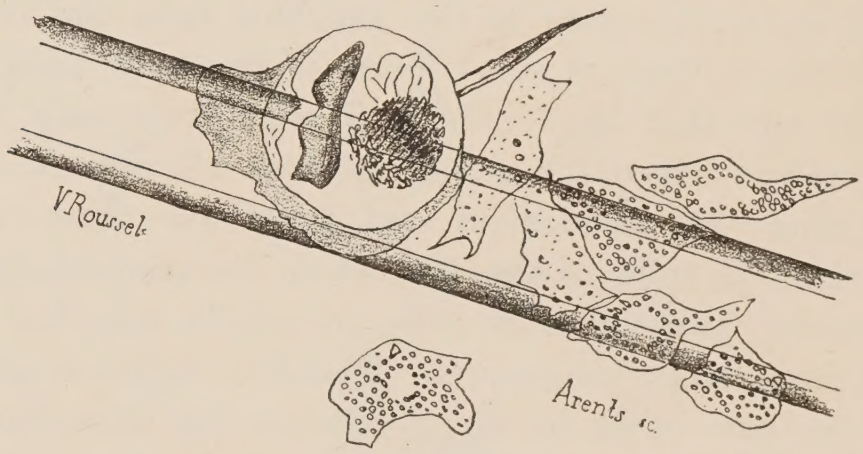

Fig. 24.—A glass tube surrounded by the mesodermic phagocytes of the Spongilla.

Spongillæ which had developed from gemmules. Like most minute particles suspended in the water, these grains were soon englobed by the Sponges and were found to have been chiefly taken up by the mesodermic phagocytes. The litmus however did not change colour, even after a prolonged stay in the cells ; hence it is evident that the digestion of the Spongillæ cannot proceed in an acid medium. This fact is in complete harmony with Krukenberg's discovery [1] of a tryptic ferment in the glycerine extract of several varieties of Sponges.

[1] "Grundzüge einer vergleichenden Physiologie der Verdauung." Heidelberg, 1882, p. 52.

If now we introduce a sharp substance, such as a minute glass tube or a spicule of asbestos, into a Sponge, the greater part of it will be situated in the mesoderm, where it will be in immediate proximity to the amœboid cells. The latter surround the foreign body either partially or completely, i.e. they react as if the substance were merely a nutritious body of larger size than

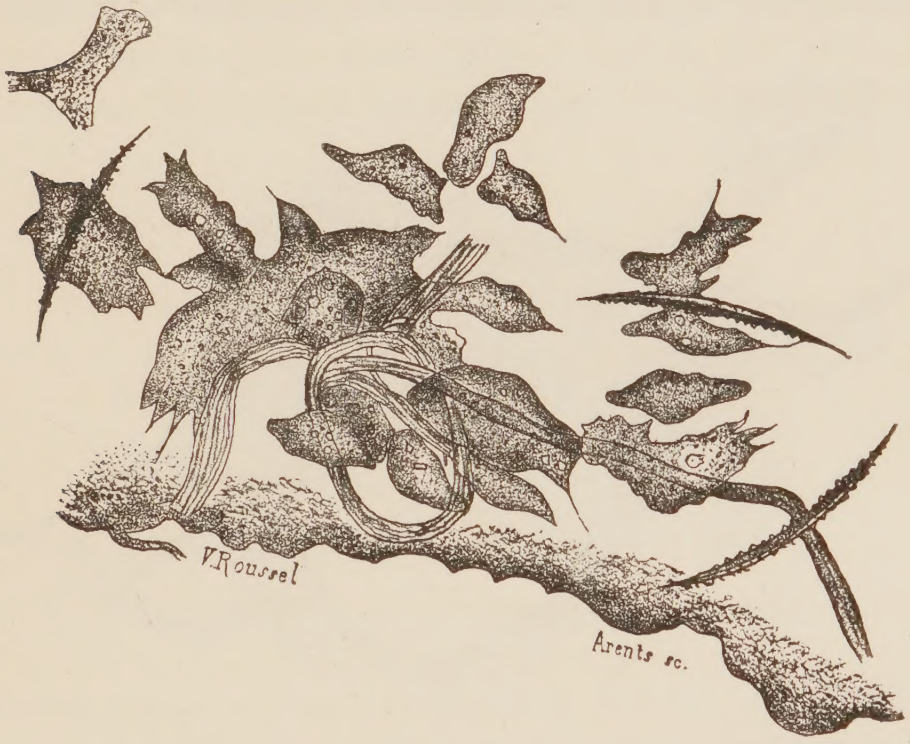

Fig. 25.—Vegetable filament surrounded by the phagocytes of a Spongilla.

usual (Fig. 24). Sometimes the cells accumulate very sparsely or not at all round the article introduced, showing that too weak a reaction has been excited. On other occasions inert bodies, such as vegetable filaments, will attract a considerable number of phagocytes which surround them and become partially fused into small plasmodia (Fig. 25).

In some members of this group the grains of sand and of other hard materials, which they happen to have

taken up, become surrounded with a mass of spongine, secreted by the mesodermic cells. In such cases the foreign particles are utilised by the Sponge to increase the solidity of its skeleton.

As I have remarked above, the mesodermic cells can also enclose living organisms which have penetrated into the interior of the Sponge, where they subsequently undergo digestion by the phagocytes. Organ-

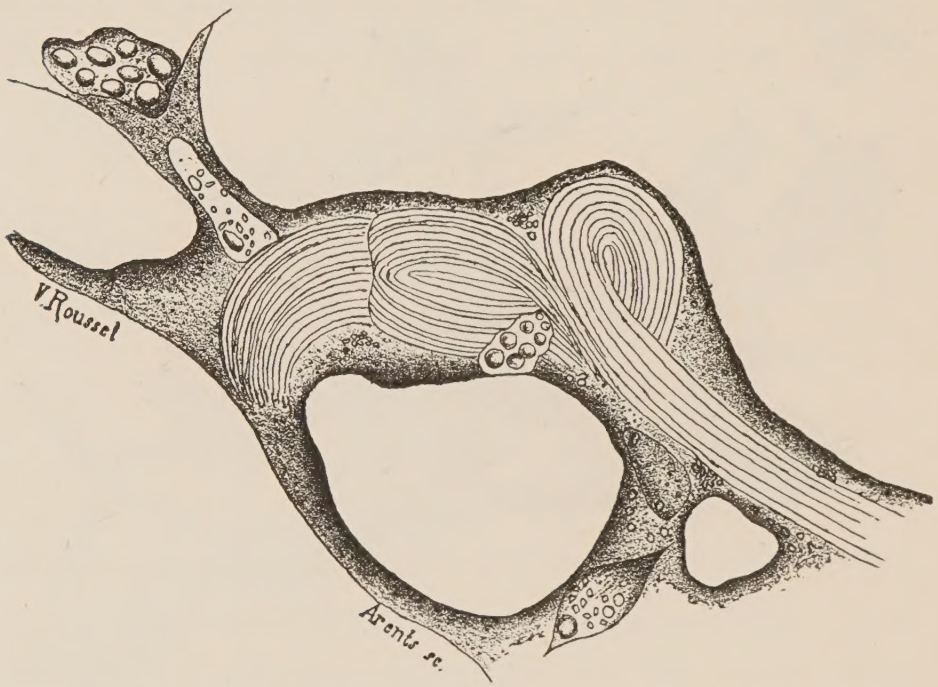

Fig. 26.—Leptotrix surrounded by the phagocytes of the Spongilla.

isms of greater resisting powers may escape this fate and may remain for a shorter or longer time within the body cavity of the Sponge without undergoing any alteration whatever. Thus I have seen filaments of Leptotrix living uninjured inside the mesoderm of young Spongillæ, and surrounded by a plasmodium formed by the fusion of a number of mesodermic cells (Fig. 26). In certain Sponges (*Hircinia echinata* and *Ceraochalina gibbosa*) Keller has found the eggs of Annelida and Crustacea developing undisturbed in the

mesoderm, and surrounded by masses of amœboid cells which formed a regular follicle round them (Fig. 27).

These facts show that any foreign body, which has by some means or other reached the parenchyma of the Sponges, excites the mesodermic phagocytes, which either englobe them, or collect in a mass or even fuse together in large numbers round them. If the foreign bodies are easy to digest, they are soon dissolved; if however they prove resistant, they remain in the in-

Fig. 27.—Crustacean ova surrounded by the phagocytes of the *Ceraospongia*. (After Keller.)

terior of the Sponge, surrounded by the cells. This phenomenon, which frequently occurs among the Spongiaria, may be regarded as an instance of a kind of commensalism. These soft cellular organisms, being readily penetrated, are very suitable as an abode for many aquatic animals on account of the continual stream of water which passes through them, bringing nourishment to their guests. Hence there are a large variety of the latter, from the Algæ (*Zoochlorellæ* and *Zooxantellæ*) which inhabit the interior of the mesodermic cells, to the Polypi (*Stephanoscyphus*), Annelida and Crustacea, which take refuge in the canals and

parenchyma of the Sponges. So far, real parasites, with the infectious diseases they bring in their train, have not been discovered. It may be that the phagocytes are so effective as to utterly destroy the microbes which enter the Sponges, or it may be that our knowledge is incomplete on the subject.

If now we consider the analogy existing between the Sponges on the one hand and the Protozoa and Myxomycetes on the other, we find that the digestive and excretory functions take a prominent part in the reaction against the foreign bodies which might injure these organisms. In the case of a sponge or of a plasmodium, this reaction consists merely in the enclosure of the particles, and their subsequent digestion, if they are digestible, or in their expulsion from the body, if this is not the case. In the Myxomycetes this function is performed by the whole of the protoplasmic contents, whereas in the Sponges it is confined chiefly to the mesoderm, though the endoderm also takes some part. The outer covering or the ectoderm generally is however not unconcerned in the work of protecting the organism against all manner of injurious agents. The flat cells of which the ectodermic layer consists, are contractile and sensitive ; by their contraction the pores are opened and allow the surrounding water to pass into the interior of the sponge, so long as this does not carry any harmful products along with it. It has long been known that in order to follow the mode by which the coloured granules penetrate into the cells to the best advantage, experiments should be made with starving specimens. As soon as the sponge is sufficiently filled with the minute particles which have been brought by the water, the pores refuse to allow the passage of any more by remaining closed.

According to de Lendenfeld, the Sponges do not open their pores to harmful substances, whether these are in solution or consist of granules suspended in the water. Of all the bodies which he made use of, such as carmine, starch, milk, the last was the only one that at once found its way inside the sponge; in the case of carmine, the pores at first remained shut, although they opened after a short while. The solutions of different toxic substances, as morphine, veratrine, or strychnine, caused contraction of the pores, which did not relax for some little time.

There is an analogy as well as a difference between the mode of action of the ectodermic cells, which are contractile although not phagocytic, and that of the plasmodia of the Myxomycetes. The analogy consists in a sensibility towards the chemical composition of the surrounding medium; the difference is shown in the manner of reaction. The mobile cellular colony—the plasmodium—is repelled from the object which calls forth the exhibition of its sensibility (negative chemiotaxis, thermotaxis or otherwise); the motionless organism—the Sponge—avoids the same object by refusing entrance to it.

In spite of the limitations of our knowledge, we are in a position to affirm that in their struggle against various injurious bodies, the Sponges make use of all their cellular properties, more especially of the sensibility and contractility possessed by the ectodermic elements, and the power of englobing and digesting common to mesodermic and endodermic cells. These results may serve as a starting-point for the inquiry into the more complex phenomena of reaction in other animals.

LECTURE V.

Cœlenterata, *Echinodermata* and *Vermes*—Traumatism and regeneration in Hydra—Accumulation of phagocytes in Acalepha (Scyphomedusæ)—Phagocytes of star-fishes—Inflammation in Bipinnaria—Reactive changes in the perivisceral cells of the Annelida—Phagocytic reaction in the diseases of Nais and Lumbricus—Struggle between the phagocytes of Lumbricus and Rhabditis—Microbic infections of Worms.

ALTHOUGH the Cœlenterata are distinguished from the Sponges by their higher organisation, yet there are a number of members of this group which consist of only two layers of cells, the mesoderm being completely absent. Since it is the mesoderm which, as we have seen in the Sponges, plays the principal part in pathological processes, it would be interesting to know how those processes are carried out in such animals as Hydra and its congeners, which have only two layers of cells.

As far back as the last century the phenomena evoked in the fresh-water Polyps by every kind of injury were often the subject of observation. Trembley first pointed out the astonishing power of regeneration possessed by this organism. A Hydra may be cut up into several pieces, pierced with pointed bodies, and in general maltreated to an extraordinary extent without preventing a speedy and complete reintegration. In one experiment of Ischikawa[1] the front part of a

[1] *Zeitschr. f. wissensch. Zoologie*, vol. xlix. 1889, p. 433.

Hydra had completely recovered within twenty minutes after the infliction of an injury. Hydræ, cut in two longitudinally, and stretched out on a cork, are able to grow again into complete animals in little more than twenty-four hours.

In another experiment Ischikawa cut off the head and tentacles of a Hydra, and made a longitudinal slit down the trunk, which he fixed on a piece of cork in such a manner that the endoderm was directed outwards. In order to injure this layer the hydra was

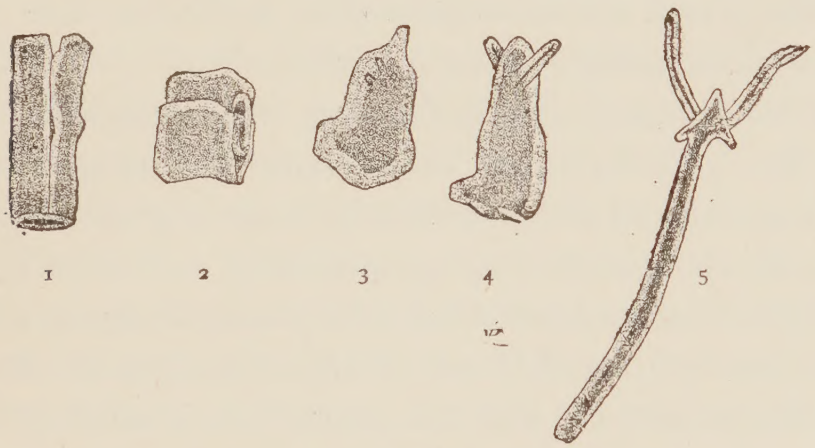

Fig. 28.—Regeneration of a Hydra (after Ischikawa).

taken out of the water in this position, and exposed to the air for five minutes. On then detaching it from the cork and putting it into the water, the Hydra first rolled itself up into a cylinder, the outer surface of which was formed by the endoderm (Fig. 28, 1); soon, however, it rolled itself in the opposite direction, so that the two layers occupied their normal relative positions. During this inversion, however, the experimenter had inserted a filament of an alga between the edges of the cut, so that they could not fuse together (Fig. 28, 2). The Hydra then changed its position, and finally grew into a closed sac (Fig. 28, 3) which acquired a mouth and tentacles and

formed a perfect Hydra (Fig. 28, 4, 5) within six days after the commencement of the experiment.

Punctures and other artificial lesions heal with extraordinary rapidity, without any accumulation of phagocytes at the injured spot. But although no accumulation takes place owing to the absence of a mesoderm, yet we must not imagine that the phagocytic function is completely wanting in these animals. The whole of the endoderm in the Hydra consists of stationary phagocytes in the form of epithelial cells, which are capable of putting out amœboid processes from their free surface, and ingesting various foreign bodies.

In the marine colony-forming Hydromedusæ, not only the endoderm, but occasionally the ectoderm as well, consists of phagocytes which are of great importance on account of their prophylactic action.[1] These creatures like the Hydra have the power of regeneration. If the head of one of these Hydrozoa, such as the Podocoryna, be cut off and the trunk left in contact with the colony, a fresh head will grow, while the detached head becomes fixed and forms a new trunk.

In all these phenomena we see a regenerative capacity of such rapidity and extent that the danger of infection becomes reduced to a minimum. We may here observe the regenerative side of inflammatory processes, but not the phenomena of inflammation itself or at least not the accumulation of phagocytes at the injured spot.

This accumulation is not however an uncommon occurrence in the Cœlenterata. Most of these animals, like the Acrospeda, the Ctenophora and the true Polyps, are provided with a tolerably well developed mesoderm,

[1] See my article in *Arbeiten des zool. Institutes zu Wien*, vol. v. 1883, pp. 143-146.

and contain in their intercellular substance a number of amœboid cells which have all the properties of phagocytes.

If we take a large Medusa, known as *Rhizostomum Cuvieri*, and introduce some pointed body, as a splinter of wood or even a pin, into its gelatinous bell, the very next day it will be perceptible to the naked eye that a cloudiness has arisen around the foreign body. This, when microscopically examined, will be found to consist of numberless amœboid cells which have collected round the seat of lesion. The same thing takes place in another of the Acalepha, *Aurelia aurita*. If the object introduced into the bell of the Medusa has been previously soaked in a colouring matter, such as carmine, the phagocytes which assemble at the injured spot will be found filled with coloured granules. The amœboid cells which accumulate around the foreign body either remain isolated or unite to form minute plasmodia.

We therefore see that in these Medusæ, which have no kind of vascular system, the mesodermic phagocytes are able to traverse a gelatinous substance, which is sometimes, as in the Rhizostomum, very tough, and to collect for the purpose of englobing the minute bodies or of surrounding the larger foreign bodies which have been introduced.

The analogy of these events with the reactive phenomena in the Sponges is obvious, although there is a considerable difference between the mesoderms in the two cases. Whereas in the Sponges, the mesodermic phagocytes by taking up solid food-particles play an important part in nutrition, in the Medusæ and in all the Cœlenterata which possess a mesoderm, the function of nutrition is exclusively confined to the endoderm.

In all the Cœlenterata this consists of a phagocytic epithelium entirely separate from the mesoderm, at any rate in the adult condition. Although deprived of their nutritive function, the mesodermic phagocytes retain their power of approaching foreign bodies, of englobing or surrounding them and of digesting some of them. This power is not only exercised on the foreign bodies which have penetrated into the Cœlenterata as a result of some lesion ; it is equally active in the case of the tissues of these animals themselves. Thus the abortive generative cells, of which there are a large number in Medusæ kept under artificial conditions, are duly devoured by the phagocytes, which surround them as with a kind of follicle. It is apparent that these mesodermic cells have not lost their primitive properties of intracellular digestion, and although they have become distinctly separated from the endoderm, the common origin of the two layers may be embryologically demonstrated.

The development of the mesodermic amœboid cells at the cost of the endoderm—which is a fact of very frequent occurrence in the animal kingdom—may be readily followed in the various representatives of the Echinodermata, especially in the sea-urchins and the star-fish. We will take a star-fish common in the Gulf of Trieste, the *Astropecten pentacanthus*, as an example. The segmented ovum becomes converted into an oval body consisting of a layer of ciliated cells enclosing a segmentation cavity. A part of these cells becomes invaginated to form the first rudiments of the intestinal canal and its appendages. The larva soon assumes the characteristic *gastrula* stage, and consists of an ectoderm, or outer layer, and of an endoderm, forming a cul-de-sac with an opening at the lower end. The space between

the two layers represents the general body-cavity and is filled with a homogeneous and semi-fluid substance, containing the amœboid cells of the mesoderm. These are merely migratory cells which have become budded off from the endodermic invagination.[1] (Fig. 29.) Almost immediately upon their arrival in the body-cavity they are able to begin their phagocytic duties. Among the numerous larvæ of the Astropecten which float on the sea, some may be found with their delicate ectoderm injured by a sharp body which has pierced the general body-cavity. (Fig. 30.) But as soon as the larva has been thus damaged, the mesodermic cells travel towards the invading object, and surround it completely by fusing into minute plasmodia. (Fig. 31.) The latter, if duly prepared in a 0·5 per cent. solution of osmic acid and stained with picrocarmine, are seen to contain a certain number of nuclei, the appearance of which shows definitely that no proliferation of cells is taking place. In these larvæ, the reaction, which can be followed step by step owing to their transparency, consists merely in an accumulation of mesodermic phagocytes around the foreign body. There can be no question here of the intervention of any vascular, muscular, or nervous systems, since in these larvæ such

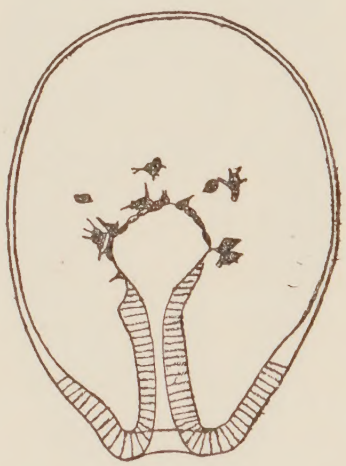

Fig. 29.—Formation of phagocytes in the larva of Astropecten.

[1] Cf. my article in the *Zeitschrift f. wissensch. Zoologie*, vol. xlii. 1885. See also the account of the discussion between Selenka and myself, and the more recent paper by Korschelt in the *Zoologische Jahrbücher*, vol. iv. 1889.

systems do not exist. The reaction is effected entirely by the phagocytes themselves, and is accompanied neither by proliferation of cells nor by increased flow of fluid to the part, as shown by the absence of œdema. The non-occurrence of proliferation is readily explicable by the fact that the foreign body on account of its minuteness has produced but a very slight lesion of the ectoderm.

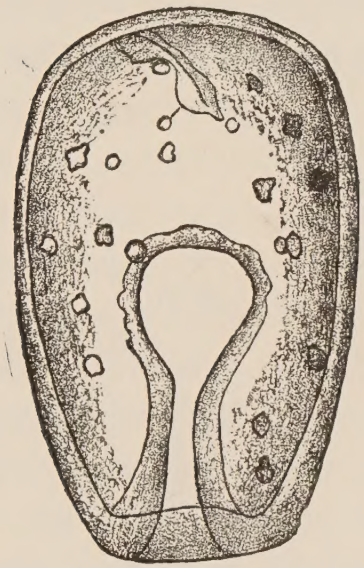

Fig. 30.—Gastrula with a foreign substance in its body-cavity.

In larvæ of more highly developed and complex organisation, the reaction takes place in the same manner. I have frequently seen a marine alga, a species of *Chætoceros* which is provided with very delicate hairs, settle on and penetrate into specimens of Bipinnaria (larvæ of Astropecten). In all these cases, the lesion was followed by an accumulation of mesodermic phagocytes together with the formation of plasmodia.

In the instances above quoted, the larvæ were too minute to admit of artificial experimentation; it was merely a question of watching the effects of lesions arising under natural conditions. But the reactive phenomena ensuing on artificial injuries [1] may be readily observed in the much larger larvæ, the *Bipinnaria asterigera*, which likewise represent a stage in the development of the star-fish. If a delicate glass tube, a rose-thorn, or a spine of a sea-urchin be introduced into

[1] See my article in the *Arbeiten des zoolog. Institutes zu Wien*, 1883, vol. v. p. 141.

one of these larvæ, the amœboid cells of the mesoderm collect around the foreign body in large masses easily visible with the naked eye. All the minute particles adherent to the object introduced, or the granules of carmine or indigo, if the object has been previously immersed in these substances, are eagerly devoured by the mesodermic phagocytes. (Fig. 32.)

If instead of these sharp solid bodies, a drop of blood be introduced into a Bipinnaria, it will be at once

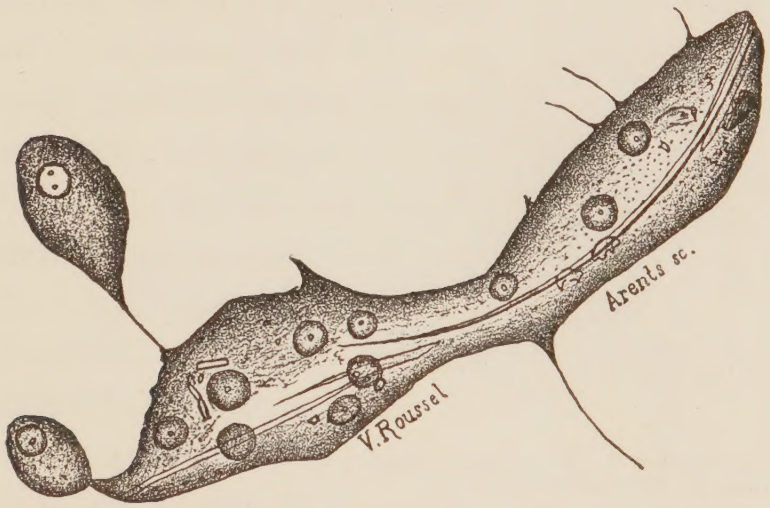

Fig. 31.—The oreign body of Fig. 30 surrounded by a plasmodium of the larva (highly magnified).

surrounded by the mesodermic cells, which will collect around the masses of blood corpuscles to form true plasmodia, that is to say, multinuclear protoplasmic masses arising from the complete fusion of the phagocytes (Fig. 33). The changes undergone by the red corpuscles of the blood within the mesodermic cells of the larva correspond exactly with the phenomena of intracellular digestion, and may be observed in the same way with the fat-globules of milk.

Bacteria if introduced into the Bipinnaria are likewise enclosed by the mesodermic phagocytes. The great

transparency of the larvæ of Echinoderms enables the observer to ascertain the fact that the bacteria are still mobile, and that they have therefore been devoured alive.

In spite of the differences which distinguish the Sponges, the Cœlenterata possessing a mesoderm, and the Echinoderms from each other, they are all essentially similar in their phenomena of reaction. In the Sponges we have a mesoderm with a plentiful supply of mobile cells which play an important part in the nutrition of these animals. The food, after entering the body, invariably reaches the mesoderm, which is intimately connected with the endoderm. In the Acalepha (Medusæ) and the other Cœlenterata in which this layer is present, the mesoderm is directly connected with the endoderm only while it is being developed. When its development is complete, the mesoderm becomes definitely separated from the endoderm and has nothing further to do with the function of nutrition, which is relegated entirely to the endodermic phagocytes. In the larvæ of Echinoderms the two layers are equally distinct from each other ; the mesoderm is likewise excluded from the office of nutrition, while the endoderm which is the sole organ of nutrition, has no power of intracellular digestion. In this animal, digestion is performed by means of ferments secreted by the endodermic cells, and poured into the intestinal cavity.

Fig. 32.—Collection of phagocytes round a splinter. *Bipinnaria asterigera.*

Now although these animals differ thus in organisa-

tion from one another, their mesodermic cells are alike in that they move towards foreign bodies, englobe and, when possible, digest them. In all of them the various lesions produced by such foreign bodies provoke an accumulation of mesodermic phagocytes, with or without formation of plasmodia or giant cells.

Moreover these animals all resemble each other in the fact that the phagocytes of their mesoderm are repre-

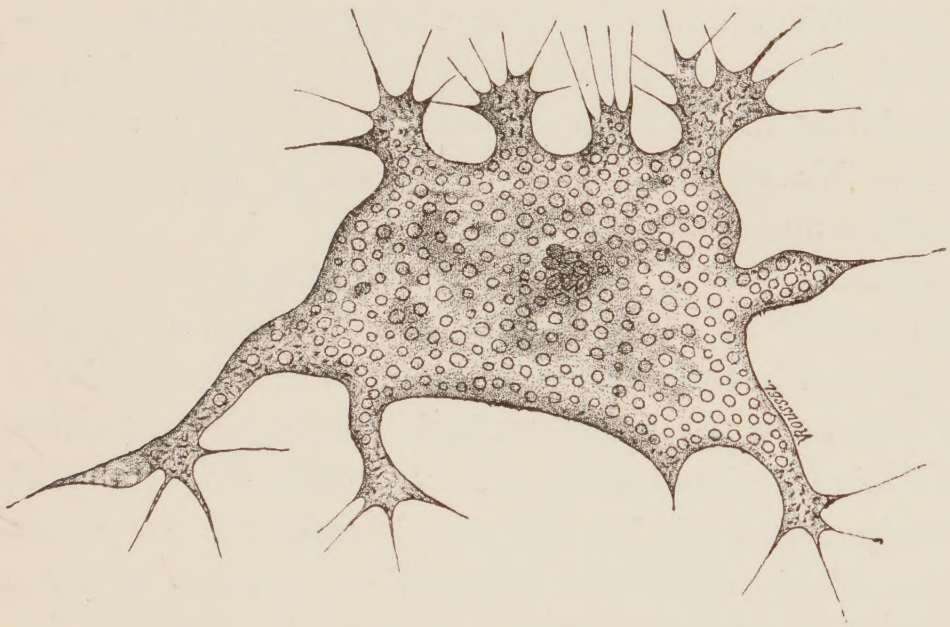

Fig. 33.—Plasmodium formed by the phagocytes of the Bipinnaria.

sented by branched connective tissue corpuscles embedded in a semi-fluid or gelatinous intercellular substance. In all the cases that we have considered, there was neither blood nor plasma, blood-corpuscles nor blood-vessels. These structures are not found either in the Sponges or in the Cœlenterata, and are only present in the Echinoderms at a later period of development than that of the specimens which served for these pathological investigations.

If now we turn our attention to the varied group of the Vermes, we shall at once meet with reactive phe-

nomena similar in character to those described above. As a representative of the lower orders of worms, we will take the transparent Turbellarium, *Mesostomum Ehrenbergi*. If we injure any part of its body, the mesodermic phagocytes will, after a certain time has elapsed, assemble round the lesion. The number of granules they contain gives them a great resemblance to the epithelial cells of the intestine which, in the Turbellaria, are likewise true phagocytes. The mesodermic cells are amœboid elements embedded in a gelatinous intercellular substance, forming a mucoid connective tissue like the mesoderm of the Sponges, Medusæ and Echinoderms.

In the higher Worms the mesodermic phagocytes are represented by the peritoneal endothelium or by cells suspended in the perivisceral fluid. These two varieties of cells have the same marked phagocytic properties, and this functional analogy may explain the fact that in closely allied species, the perivisceral cells are sometimes highly developed while at other times they are completely absent. These mesodermic elements besides fulfilling their phagocytic duties, act as respiratory and excretory organs.[1]

If a splinter be introduced into the perivisceral cavity of an Annelid, such as the *Terebella*, it will be soon covered with a thick layer of these 'lymphatic' cells, the phagocytic properties of which are shown by the readiness with which they take up the minute grains (of colouring matter or otherwise) attached to the splinter. This is the more interesting, since the

[1] See Grobben, "Die Pericardialdrüse der chætopoden Anneliden." *Sitzungsberichte der k. Akad. d. Wissensch.*, Wien, vol. xcvii., 1888.

majority of the Annelida are endowed with a highly developed and completely closed vascular system. The reaction to foreign bodies is however confined to the mesodermic phagocytes, the vessels taking no part whatever in the process, as may be readily seen owing to the bright colour of the blood in them.

The same phenomena occur in the Annelida which

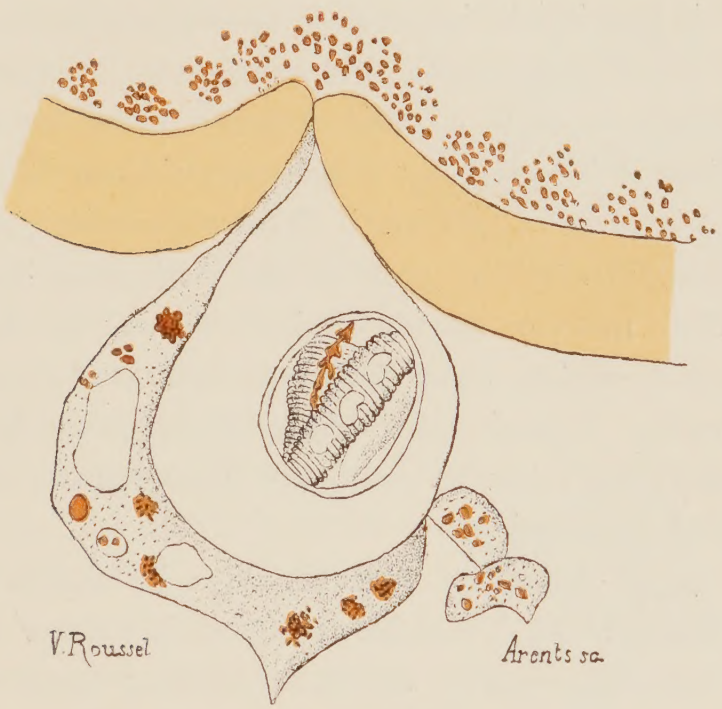

Fig. 34.—A larva of *Gordius* encysted and surrounded by a plasmodium in a specimen of *Nais*.

have a well-developed vascular system, but no perivisceral leucocytes. If a certain number of *Nais proboscidea* be examined, some of the individuals will be found to be infected with larvæ of *Gordius*, which after entering the general body cavity, excite phagocytic reaction of the peritoneal cells alone. The latter send out protoplasmic processes and form minute plasmodia around the larvæ, which protect themselves by secreting a chitinous covering and enclosing themselves in a sort of cyst. Although these cysts with their surrounding

plasmodia are sometimes found in close proximity to the vessels, the latter do not react in any way to the presence of the parasite. (Fig. 34.) If any exsudation from the vessels took place into the interior of the plasmodium, it would be at once evident, since the blood-plasma is yellow while the perivisceral fluid is perfectly colourless.

As it is manifestly impossible to experiment upon the minute *Nais proboscidea*, the phagocytic properties of the peritoneal cells of this Annelid must be studied in specimens infected by a microsporidium belonging to the microbes of '*pébrine*.' These parasites excite a similar reaction on the part of the peritoneal endothelium, the minute spores being taken up by the phagocytes which have become separated from the peritoneum. Occasionally these spores may be seen surrounded by vacuoles as in the most typical cases of intracellular digestion.

The larger Annelida may likewise be employed for these researches. Valuable information may be obtained from the study of the common earth-worms, which are frequently invaded by parasites. Among these the most frequent and also the best known are the Gregarinæ belonging to the genus Monocystis, which attack the male organs. When once inside the latter, these mobile Protozoa have to encounter a large number of amœboid cells, which are among the most active of phagocytes. They are provided with slender and membranous protoplasmic processes (Fig. 35, A), and devour with the greatest eagerness all foreign bodies which come in their way. Even when examined in the aqueous humour of the rabbit or other inert fluid, these cells give evidence of their phagocytic activity by

englobing grains of colouring matter or any other minute bodies that may have been added to the preparation. If they meet with a larger object, such as a thread of cotton, they will collect in groups and finally surround it with their protoplasm. (Fig. 35, B.) Now these same cells react to the parasites which have penetrated the earth-worms. While the Gregarinæ are in their condition of activity, they repulse the phagocytes by the violence of their movements so that the latter are rarely able to fix themselves on the parasite. But as soon as it attains the quiescent state, the phagocytes adhere to its surface, frequently collecting to form a dense mass around it. The Gregarina evidently objects to this living covering and seeks to defend itself by the secretion of a cystic membrane. (Plate II., Fig. 1.) Thus protected, it begins to produce spores by dividing into a large number of increasingly smaller oval bodies, and gives rise to the pseudo-navicellæ which have been so often described. The mass of surrounding phagocytes continues however to act upon the parasite and frequently succeeds in injuring and even in killing it. The encysted Gregarina goes on defending itself by means of chitinous secretions which assume exaggerated proportions and become fringed with irregular processes,

Fig. 35.—A. Phagocyte of *Lumbricus*. B. Collection of phagocytes of *Lumbricus* round a foreign body.

presenting a strikingly abnormal appearance. (Plate I., Fig. 2.) Finally the whole interior of the encysted Gregarina becomes highly refracting, and the parasite dies, leaving the phagocytes the masters of the day. (Plate I., Fig. 3.) The phagocytes themselves undergo marked alteration around the parasite and, losing their power of movement, are converted into flat closely apposed cells. (Plate II., Fig. 1, 2.) Sometimes the capsule thus formed, which has the same structure as connective tissue, remains very thin; but it usually becomes thickened by the further addition of fresh

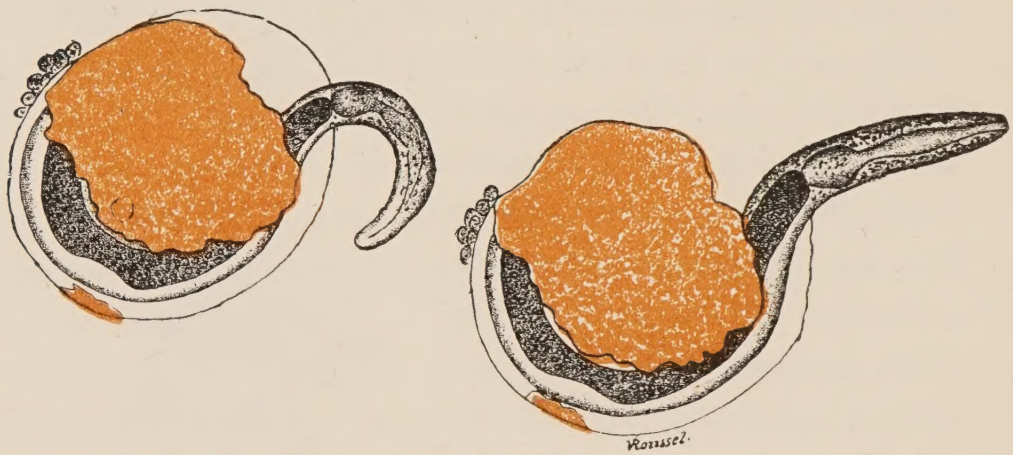

Fig. 36.—A live Rhabditis surrounded by a mass of the phagocytes of Lumbricus.

layers of cells. Among these may be seen some which are deeply pigmented with a brown colour. During the whole course of the struggle between the parasite and the phagocytes of Lumbricus, the blood-vessels although highly developed remain quite passive, that is to say, there is no visible change in their volume, nor any exsudation of the reddish plasma.

The spermathecæ of Lumbricus as well as its general body cavity, may also be invaded by Nematoda belonging to the genus Rhabditis. The latter, in spite of their size and mobility and the toughness of their cuticle, have likewise to do battle with the

numerous phagocytes of the earth-worm. These cells surround the Nematode forming a thick capsule round it like that which is produced round the Gregarina. Microscopical examination of the Rhabditis in this condition proves directly that the phagocytes have enclosed it while still alive, as it may be seen moving in the midst of the mass of cells. (Fig. 36.) The worm, thus confined in its movements, secretes layers which form, not a true cyst, but a supplementary cuticle which frequently becomes of extraordinary thickness. (Plate I., Fig. 4.) This abundant secretion evidently

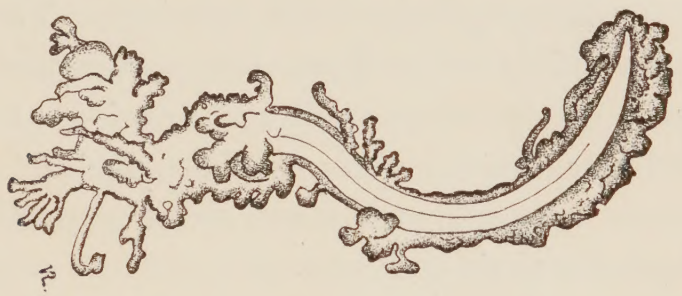

Fig. 37.—A Rhabditis without its phagocytic covering in order to show the cuticular processes.

exhausts the parasite, for it loses the granules of fat with which it was at first filled and becomes quite transparent. (Plate I., Fig. 5.) The chitinous layers, as they become thicker and thicker, finally form irregular processes, which give a strange abnormal appearance to the Rhabditis. (Fig. 37. Plate I., Fig. 4.) In isolating the collections of phagocytes enclosing the worm with its thickened cuticle, it often happens that the Nematode manages to escape, leaving its cuticle in the mass of cells. On the other hand, if the contents of the male organs of Lumbricus be examined, there will frequently be found situated in the midst of phagocytic capsules, highly refracting bodies, which may readily be identified as the shapeless cuticular

layers and the remains of the Nematode buried in the products of its own secretion.

Here then we have an example of a struggle between two members belonging to the same group of the animal kingdom. The Nematode worm protects itself by means of cutaneous secretions; the earthworm fights by means of an army of mobile cells, endowed with phagocytic properties. It is evident that the latter greatly embarrass the parasite by surrounding it with their solid masses, although we do not yet know the exact nature of the harmful influence exercised by the phagocytes on the intruder. They may act by preventing the inflow of nutritive material or of oxygen, or by means of an injurious secretion. These delicate points can only be decided by the most minute research, and must await a perfection of our methods for their final answer.

At present we must be satisfied with the statement that Lumbricus, like the Annelida generally, reacts to various infective agents by means of the phagocytes of their perivisceral fluid without any intervention on the part of the blood or of the highly developed blood-vessels. This reaction takes place in the same way against Gregarinæ as against Nematoda. In speaking of the latter, I must particularly mention the fact that they are devoid of migratory cells. The phagocytic system of the Nematoda is probably reduced to the muscular phagocytes, which are formed in a very curious manner. These animals protect themselves by the secretion of tough membranous cuticles, resembling in this feature the plants, the cells of which are likewise protected by thick resistant membranes. This analogy is borne out by the fact that

these animals, like plants, are very frequently attacked by parasitic fungi, which are enabled to penetrate the cuticle by their great power of growth and also by the secretion of ferments which can dissolve the most impervious substances, such as cellulose.

Among the infectious diseases of the Nematoda, we must name one which is produced by the parasitism of one of the Mucorineæ (*Mucor helminthophorus*, De Bary), which invades the intestine and the genital organs of the Ascaris of the cat (*A. mystax*),[1] as well as the frequent infections of the free Nematoda by several other members of the class of fungi. The most remarkable is certainly the *Arthrobothrys oligospora Fres.*, because, according to Zopf,[2] this mould catches the Anguillulides with hooks, and afterwards penetrates their bodies with its filaments. Once inside, the fungus grows freely in the body cavity and causes complete fatty degeneration followed by death of the animal. There is finally nothing left of the Nematode but its cuticle and the chitinous covering of the male genital organs.

Besides these epidemics, occasioned by the higher fungi, the Nematoda are liable to invasion by Chytridiaceæ and other inferior organisms, allied to those which infect the nucleus and nucleolus of the Paramæcia.[3]

This survey of the pathological phenomena in Cœlenterata, Echinoderms and Worms, has shown

[1] *Zeitschrift f. wissensch. Zool.*, 1862, vol. ii. p. 135.

[2] *Nova acta Acad. Leopold*, vol. xlvii. p. 167; and "Pilze," 1890, p. 240.

[3] See Bütschli, "Studien über die ersten Entwickelungsvorgänge der Eizelle." Frankfürt, 1876, p. 360.

that some of these animals react chiefly by the rapid and active regeneration of the injured parts, while others protect themselves by secretions of chitinous layers. These two methods, however, only hold in certain cases, whereas the usual mode of reaction, to which there are but few exceptions, is by means of amœboid and mobile cells which accumulate around the injurious body and either surround it entirely or englobe it. The reaction is effected through the sensibility of the phagocytic cells themselves, and is in no way influenced by the nervous or vascular system. In all the above-mentioned cases, the phagocytes were mobile connective tissue cells, or cells of the perivisceral cavity. So far we have not discovered any instance of phagocytic action on the part of the blood-corpuscles. It is true that our observations have been confined to animals which have no formed elements in the blood. Annelida with white corpuscles in their blood do not often occur, and even in cases where these are present, their number is small, and certainly less than the amount found in the perivisceral cavity.

LECTURE VI.

Arthropoda, Mollusca, and Tunicata—Their vascular system—Their Phagocytes—Spleen of the Gasteropoda—Inflammatory reaction—Diapedesis in intact Ascidians—Introduction of bacteria into the body of Ascidians and Crustaceans—Infectious disease of sandhopper (Talitrus)—Diseases of Daphnia —Introduction of bacteria into insects—Epidemics among insects.

A LARGE number of the invertebrata possess blood-corpuscles in the form of colourless cells which float in the blood-plasma. The circulation of this fluid is effected by the movements of the heart, which is always present. In these animals—Arthropoda, Mollusca, and Tunicata—the vascular cavity is identical with the general body cavity. In the lower representatives of these types (we disregard certain groups without a trace of a vascular system, such as many of the Copepoda, Ostracoda and others) the only vascular organ present is the heart, in the form of a simple sac or tube open at its extremities to expel the blood and provided with lateral apertures for the entry of this liquid. To this central organ are soon added one or several principal arteries which open into a system of lacunæ, in which the blood circulates before going back to the heart. In the invertebrata rather higher in the scale, especially in the Mollusca, we find also a venous system, which is sometimes, as in the Cephalopoda, very highly

developed. But in all cases without exception, even when a large number of vascular ramifications are formed, there is a network of lacunæ between the arterial and venous systems. These lacunæ are filled with blood and are remains of the general body cavity.

The blood-corpuscles with a few rare exceptions are represented by colourless cells, possessing one or rarely two nuclei and a protoplasmic body capable of amœboid movements. In many invertebrates there is only one variety of mobile blood-corpuscles, containing a few sparse granules, whereas in certain others, such as many insects and molluscs, two varieties occur—granular leucocytes, with a large number of coarse granules, and hyaline leucocytes, with few or no granules. The latter kind is the one which will interest us most.

The leucocytes of Arthropoda, Mollusca, and Tunicata are in most cases amœboid and phagocytic cells, and differ from the white corpuscles of vertebrates in having a single round or oval nucleus, which is not lobed. In the invertebrates now under consideration no multinuclear leucocytes exist, nor do we find in them a vascular system with complete capillary blood-vessels.

The leucocytes of the three types just mentioned manifest pronounced phagocytic functions. It was in a representative of these invertebrate groups that the discovery was first made (in 1862) that leucocytes possessed the power of taking up foreign bodies into their interior. Hæckel[1] showed that, after injecting the mollusc Thethys with indigo, granules of

[1] "Die Radiolarien," 1862, p. 104.

this colour were to be found within the blood-corpuscles. Experiments with several other species led him to the conclusion that this was a fact capable of general application—a deduction which has since been confirmed by several observers. It is therefore very surprising that a recent author, Griesbach,[1] should throw doubts on the occurrence of phagocytosis in the white corpuscles of the acephalous Molluscs. Since he did not succeed in observing any considerable taking up of a powder after injecting it mixed with water, Griesbach concludes that under normal conditions phagocytosis does not occur at all in these animals. It is very probable that the unsatisfactory results of this author were due to the fact that he used too much water to dilute the powder, and so caused the leucocytes to swell up. If we proceed more carefully, it is easy to show that in the Molluscs, as in so many other animals, the leucocytes take up greedily any solid bodies with which they happen to be in contact. The transparent Molluscs such as Phylliroë, which admit of direct examination under the microscope in the living condition, form very convenient objects for these researches.

In some gasteropod Molluscs, we find in addition to the white corpuscles, a special variety of phagocytes which form a kind of spleen in these invertebrata. This important fact has been recently discovered by A. Kowalewski,[2] who has shown that solid bodies, injected into the blood of the Pleurobranchæa and several other species (Philina, Gasteropteron, Doris),

[1] *Archiv f. mikroskop. Anatomie*, vol. xxxvii. p. 86.

[2] *Mémoires de la Société des Naturalistes de la Nouvelle Russie*, vol. xv., 1890 (in Russian).

accumulate in a certain organ which was first described by de Lacaze-Duthiers under the name of "glande indéterminée." The cells of this 'spleen,' as Kowalewski has established, deovur and digest a large number of foreign bodies such as blood corpuscles, yolk granules, and milk corpuscles.

The phagocytes, so universally present in the invertebrata which form the subject of the present lecture, react to all sorts of lesions, whether these are artificially or accidentally produced in these animals. We often come across transparent Crustacea, such as Daphnia or Branchipus, with brown spots on their sides, due to bites inflicted by other individuals. Underneath these eschars we generally find a mass of leucocytes, which remain heaped together at the injured spot until the wound is completely cured.[1] If we carefully inflict a small injury on one of these animals and observe it under the microscope, we see the leucocytes making towards the affected spot, where they take up their abode. A convenient object for experiments of this sort is furnished by the caudal appendages of Argulus, in which the leucocytes collect directly after the production of the artificial lesion (Fig. 38).

Fig. 38.—Inflamed cauda appendage of Argulus.

We may also introduce fairly large foreign bodies, such as wooden splinters, into the larvæ of various Coleoptera (cockchafer, Oryctes and others), into

[1] The extremely rapid regeneration of the epidermis in the Arthropoda causes their wounds to heal very quickly.

molluscs such as Thethys or Phylliroë or into Ascidians.[1] In all these cases a great number of leucocytes may be seen to collect around the foreign body, devouring any little fragments or granules as, for example, carmine, that may have been introduced with it.

In all cases then a phagocytic reaction is produced by the introduction of a foreign body, the leucocytes either forming a capsule round the intruder, or infiltrating all the surrounding tissues. In this exsudative and inflammatory reaction, which is often accompanied with the formation of giant cells, diapedesis can play no part, for the simple reason that in the Arthropoda and Mollusca there is no closed vascular system properly speaking, the blood cavities being merely part of the general body cavity.

In the invertebrata only one single example of diapedesis occurs ; but this is of so interesting a character that it deserves a detailed description. The Ascidians are covered with a mantle or tunic which is situated outside the epidermis. This tunic, which is composed of cellulose and is often very thick, contains a large number of amœboid cells with mobile processes. Since it is situated outside the epidermis, it was generally regarded as a cutaneous secretion containing cells of ectodermic origin. Later researches by Kowalewski[2] have shown that this view was unfounded, and that the cells in the tunic of Ascidians are in reality nothing else than emigrated leucocytes which have wandered through the epidermis. These cells of mesodermic origin are very active phagocytes, and are capable of devouring all sorts of solid bodies, including organs

[1] See the *Arbeiten des zoolog. Inst. zu Wien*, vol. v., 1883, p. 153.

[2] *Loc. cit.*

that are undergoing atrophy. Insertion of splinters into the tunic of Ascidians provokes an accumulation of these phagocytes, so that a sort of infiltration of the tunic is produced.

We have here an example of diapedesis taking place under normal conditions through the epidermis, quite independently of any inflammation ; though this latter process is also carried out by the aid of the same phagocytes, which collect around the offending particles.

Lubarsch [1] has confirmed the observation that the mobile cells in the tunic of Ascidians congregate around foreign bodies that have been introduced by a puncture. He was not so successful in his experiments on the inoculation of various Ascidians with the bacilli of anthrax. The bacteria which had been introduced into the tunic were only partially taken up by the phagocytes, while those which escaped this fate nevertheless showed marked signs of degeneration. As Lubarsch did not investigate the direct influence of the fluid portions of the tunic on the bacteria, we cannot form any definite conclusion from his none too numerous experiments. In considering them we must not lose sight of the facts that they were carried out in the month of March, when the low temperature might have had an injurious influence on the leucocytes, and that the tunic of Ascidians cannot afford a very favourable soil for the growth of bacteria and the production of their toxines.[2] Lubarsch [3] has also made some

[1] "Untersuchungen über die Ursachen der angeborenen und erworbenen Immunität." Berlin, 1891, p. 75.

[2] I must here mention the fact that the tunics of compound Ascidians such as Botryllus, often show phagocytes filled with various bacteria, even when the animals are examined immediately after being taken from the sea.

[3] *Loc. cit.*, p. 77.

similar experiments on "marine Crustacea" without any better result. The experiments are recorded very shortly, so that it is impossible to criticise them. We have a number of facts, however, which prove in the clearest manner the pronounced phagocytic properties possessed by the leucocytes of different Crustacea. By the introduction of a parasitic fungus (allied to Oïdium) into the body cavities of sand-hoppers (Talitrus), Hermann and Canu[1] have succeeded in producing a disease, which is almost always fatal to these Crustacea. The development of the parasite excites reactive changes on the part of the organism, as shown by a pronounced phagocytosis of the leucocytes. The authors describe these changes as follows: "On the seventh day, the blood, which up to this time has been quite clear, becomes appreciably opalescent, and the disorder becomes more marked on the eighth and ninth days, as the parasites increase in number. This is also the period at which the most active phagocytosis is observed; if the blood, fixed by osmic acid vapour and stained with picrocarmine, be examined under a high power, the microbes are seen to be enclosed in the corpuscles, the number in each corpuscle varying from one to twenty. In the protoplasm they are seen to be in various stages of digestion; they become paler and less highly refracting at the same time that they increase in size, chiefly in consequence of a swelling up of their enveloping membrane. Finally the place they occupied in the cell is marked only by a sort of colourless vacuole which preserves for a considerable time the elongated shape of the parasite." Besides the blood-corpuscles, the cells

[1] *Comptes rendus de la Société de Biologie*, 1891, p. 646.

surrounding the arteries also take part in devouring the parasitic fungi, thus acting as phagocytes, although they are not able to digest their prey. In the end, therefore, the parasite gains the upper hand and brings about the death of the sandhopper.

Luminous bacteria also, as Giard and Billet have shown, live as parasites on the same species of Amphipoda.

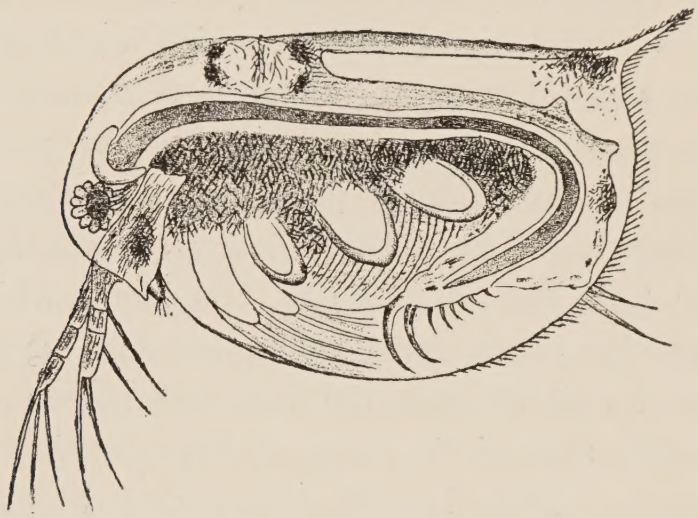

Fig. 39.—Daphnia infested by Monosporæ.

A large number of the Crustacea are subject to various infectious diseases which form an interesting subject of study from the pathological point of view, and especially on account of the light they throw on the problem of inflammation. The Daphniæ afford especially convenient objects for these researches, in consequence of their transparency and minute size, and the frequency and variety of their diseases. Among the latter we find infectious maladies produced by bacteria, Sporozoa or Saprolegniæ. The most interesting of these, however, is certainly that provoked by the presence of a fungus multiplying by budding, *Monospora*

bicuspidata.[1] This is a sort of yeast, which is found in abundance infesting *Daphnia magna* in Paris (in the reptile tank of the Jardin des Plantes) and its environs.

Among the numerous individuals of this Crustacea, we come across specimens distinguished by their milk-white colour. On examining these under the microscope, we see that their body-cavity is almost entirely filled with small needle-shaped bodies, either floating freely or adhering to the walls of the heart (Fig. 39). A close inspection shows at once that we have here very long spores, enclosed in a capsule (Fig. 40, 5). By the side of these mature spores, elongated cells and oval conidia are seen multiplying by budding, exactly in the same manner as the yeasts. (Fig. 40, 1-4.)

Fig. 40.—Monospora in various stages.

1. Young conidium.—2, 3. Budding conidia.—4. Elongated conidium.—5. Spore.

A Daphnia, once invaded by these parasites, always dies, and its body is found filled with ripe spores. Other Daphniæ, feeding on every sort of detritus which they find at the bottom of the water, devour the needle-shaped spores, and thus infect themselves through their alimentary canal. In the intestine the spores lose their capsule, and penetrate the wall so as to lie partly or entirely in the general body-cavity of the Crustacea. Directly the spore, however, appears outside the intestinal wall, it is attacked by leucocytes, which are

[1] *Virchow's Archiv.*, vol. xcvi. p. 177.

carried to the spot by the blood-stream. These cells fix themselves on the spore, forming around it a collection of cells, which often fuse together into a plasmodium. Under this influence the spore undergoes a series of remarkable changes. On being enclosed in the leucocytes the spore first loses its regular contour, becomes sinuous, and finally breaks up into a mass of brownish granules in which it would be impossible to recognise the degenerated spores if we had not studied the mode of their formation. (Fig. 41, 1-4.) The proof that this degeneration is really due to a phagocytic influence is furnished by those cases in which only half a spore is surrounded by leucocytes, the other half being embedded in the intestinal wall, or even projecting outside the skin of the animal (Fig. 41, 5). In these cases it is only the half surrounded by the phagocytes that undergoes the changes just described, while the other half, which is not exposed to the influence of these cells, remains perfectly normal.

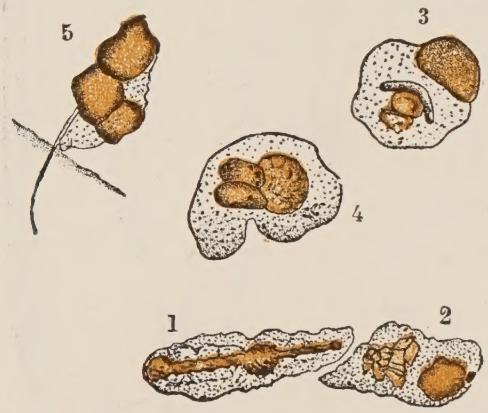

Fig. 41.—Spores of Monospora, surrounded by the leucocytes of Daphnia.

When a large number of spores penetrates the body cavity of the Daphnia at one time, the leucocytes congregate round them, in a manner resembling an infiltration or a cellular exsudation (Fig. 43, *a*). It is in fact a sequence of events exactly similar to that which we have seen produced by a traumatic lesion.

Fig. 42.—Elongated conidium of Monospora surrounded by two leucocytes.

The phagocytic action of the leucocytes, so evident and easily studied in the transparent Daphniæ, destroys the spores of the pathogenic microbe and prevents their development, thus protecting the invaded organism. I have succeeded several times in isolating infected Daphniæ and keeping them till they were fully restored

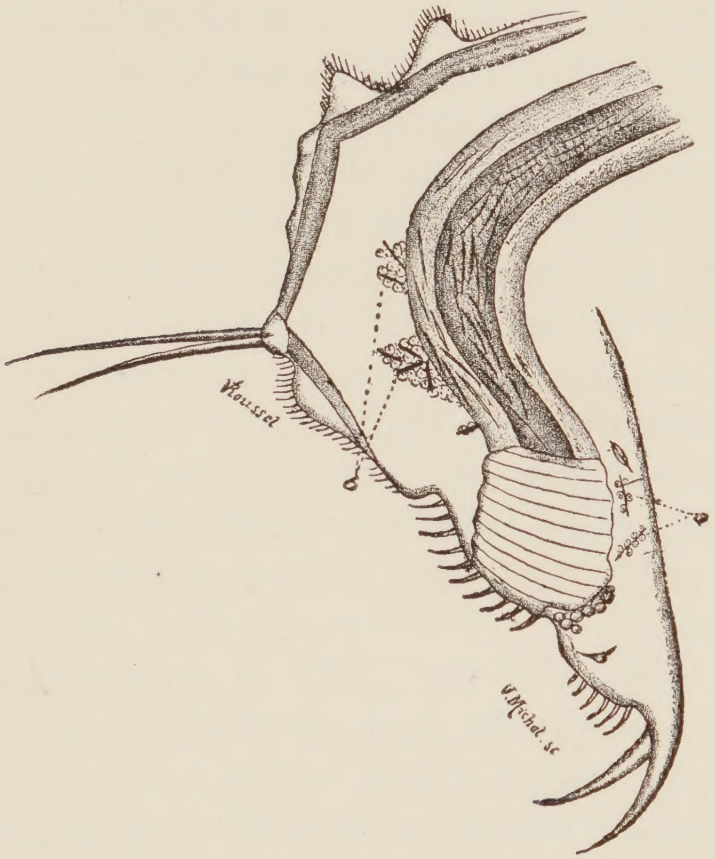

Fig. 43.—Hind part of a Daphnia.
a. Spores of Monospora surrounded by a mass of leucocytes.

to health, thanks to the destruction of the spores by their phagocytes. If on the other hand the phagocytic action is inadequate, owing to the continued increase in the number of spores swallowed or for any other reason, the latter begin to germinate and give rise to budding conidia. Although the parasite in its vegetative form is also attacked by leucocytes, it obtains the upper hand and the Daphnia inevitably

succumbs in a short time to its attack. This is owing to the fact that the conidia multiply too rapidly, and also secrete some poison which dissolves the leucocytes. Towards the end of the disease nothing but conidia are to be seen circulating in the body of the Daphnia, all the leucocytes having completely disappeared.

There can be no doubt that the whole history of this disease of the Daphniæ may be summed up as a struggle between two living organisms, the parasitic cells and the phagocytes. In spite of the extraordinary activity of the former, it is the Daphnia in most cases which, under the protection of its phagocytes, gains the upper hand. We can in this way explain the fact that even when an epidemic of Monospora is raging in a tank or aquarium containing Daphniæ, the number of these remains as high as ever. While some individuals die every day, stricken with the disease, the rest resist its ravages and multiply, thus filling up the gaps caused by the deaths.

Very different is the course of the diseases caused by parasites which do not meet with any resistance on the part of the leucocytes. To this class belong the Saprolegniæ. The spores of these fungi germinate on the surface of Daphniæ or other Crustacea (as e.g. Branchipus) and put forth filaments which penetrate into their body. The filament to effect an entry often makes use of the little fissures or orifices produced by various causes, which may be wounds or little canals pierced by the spores of Monospora. Once inside the body cavity of the Crustacea, the Saprolegnia continues its development in the blood with which this is filled, meeting with no obstacle from any side. The leucocytes manifest great indifference towards the developing

mycelium, which in the end dissolves these cells and inevitably brings about the death of the infested animal. If an epidemic of Saprolegniæ has once broken out in an aquarium, we may be quite certain that it will not stop until it has destroyed the whole of the specimens of Daphniæ or Branchipus present.[1]

Several of the diseases of Daphniæ, such as those caused by the bacteria *Pasteuria ramosa*[2] or *Spirobacillus Cienkowskii*[3] or by the Sporozoa (*pébrine* and others), meet with but feeble resistance on the part of the phagocytes. As we should expect under the circumstances these diseases, when once established, are never cured, and infallibly end in the death of the animals attacked.

The feebleness of the phagocytic protection which is so striking in Crustacea, is probably connected with the thickness of their cuticular envelopes, which clothe not only the external surface but also the intestine in these animals. The chitinous cuticle is very tough and is quite impermeable to most microbes. Thus we see that the small Crustacea, such as certain Copepoda, which are provided with a very hard covering, can get on perfectly well without phagocytes, and in fact do not possess any corpuscles at all in their blood.

The insects, so for as concerns inflammation and resistance to microbic infection, are exactly similar to the Crustacea. Every kind of lesion produces in them an accumulation of leucocytes round the injured spot, as may be easily seen on cauterising the tips of the caudal

[1] Branchipus and Artemia are subject to the disease produced by the Monospora. The pathological phenomena in these cases need further investigation.

[2] *Annales de l'Institut Pasteur*, 1888, p. 165.

[3] *Ibid.*, 1889, p. 265.

appendages in the larvæ of Ephemeridæ or other insects.

Balbiani[1] has published some very interesting researches on the effects of introducing bacteria into the bodies of various insects and Arachnidæ, and has found that many saprophytic bacteria are pathogenic and even fatal for a large number of these Arthropoda. But while the insects rich in leucocytes, (such as certain Orthoptera, especially the Gryllidæ,) can completely withstand the introduction of a great number of bacilli, the other kinds that are poor in blood and leucocytes (such as the Lepidoptera, Diptera, and Hymenoptera,) are extremely susceptible to infection by the saprophytic fungi. The power of resistance possessed by the insects belonging to the first order "must be ascribed to the action on the bacilli exercised by two varieties of cells. The first of these is represented by the blood-corpuscles which, by means of their pseudopodia, seize on the bacilli floating in the blood and include them in their protoplasm, where they are quickly destroyed ; the second variety, the elements of the pericardial tissue, consists of large cells with multiple nuclei, which surround the heart or dorsal vessel in the form of plates or cords of cells, and are more or less highly developed in different types. Of all the tissues of the body, the pericardial tissue is the only one that has the power of arresting the bacilli carried by the blood, and of taking them into their protoplasm, where they are destroyed as rapidly as in the blood-corpuscles."[2]

The insects, although so susceptible to infection by the most widespread and apparently inoffensive of bac-

[1] *Comptes rendus de l'Academie des Sciences*, vol. ciii. p. 952.

[2] *Loc. cit.*, p. 953.

teria, are nevertheless very rarely subject to epidemics of bacterial origin. The cause of this is probably to be sought in the fact that the bacilli lack the means of getting through the thick cuticular wall which covers the skin and lines the intestinal canal and tracheæ of insects. Besides the lethargy of silkworms ('flacherie'), discovered by Pasteur,[1] in which infection takes place through the intestine, there are certain other diseases of insect larvæ which are occasioned by bacteria. Thus the larvæ of *Anisoplia austriaca* in the south of Russia are sometimes invaded by a bacillus which, in its length and curved shape, recalls the appearance of the anthrax bacillus. At the beginning of the disease the affected larvæ are not to be distinguished from normal individuals, and it is only after the complete invasion of the blood that they show signs of illness and shortly afterwards die.

These diseases, however, are not nearly so frequent as those caused by the higher fungi or by the Sporozoa, which are much better adapted than the bacteria for penetrating the chitinous coverings of insects. In the strength of their growth the former possess a powerful means whereby to penetrate the cuticular walls, while the Sporozoa have an amœboid stage during which, by virtue of their mobility, they are able to effect an entry at even the most protected spots.

An observation of de Bary[2] on the conidia of *Cordiceps militaris* that had been englobed by the leucocytes of caterpillars, leads us to conclude that the conidia of fungi which multiply in the insect blood,

[1] "Études sur la maladie des vers à soie," 1870, vol. i.

[2] "Vergleichende Morphologie und Biologie der Pilze," 1884, p. 399.

sometimes meet with a certain amount of resistance on the part of the phagocytes. But in the majority of cases that have been examined to decide this point, the mycelial filaments and conidia develop in the blood without check or hindrance. I can vouch for this especially in the case where *Cleonus punctiventris*, as larva, chrysalis or perfect beetle, is invaded by the *Isaria destructor*. The oval green spore germinates on the surface of the body, and gives rise to a small filament. This latter experiences great difficulty in pene-

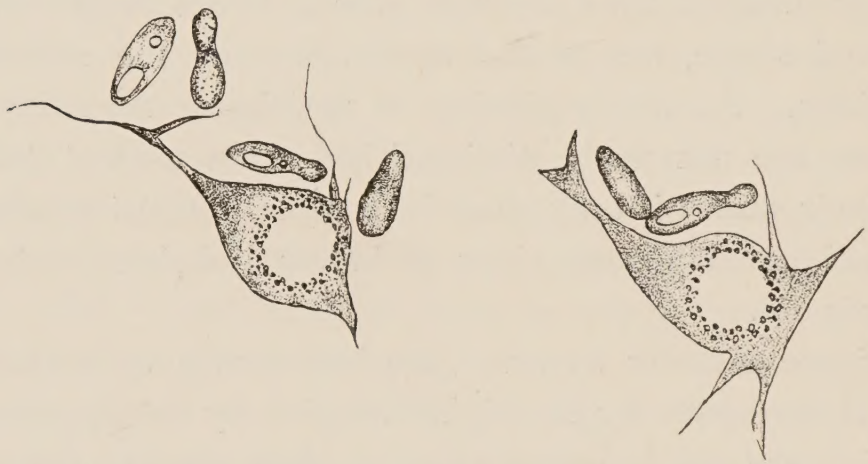

Fig. 44.—A leucocyte of *Cleonus*, showing two phases of movement. The conidia of *Isaria* lie by its side, and are not englobed.

trating the cuticle, which becomes brown round the puncture made by the parasite. But as soon as this obstacle is overcome, the filament gains access to the body cavity where, bathed in the blood, it grows freely. The leucocytes at times approach the filament or detached conidia, but do not englobe a single one of these parasites (Fig. 44, 45). The latter therefore speedily invade the whole animal and transform it into the hard mass, so characteristic of the dead bodies of the insects that have perished from one of the varieties of 'muscardine.' These pests, which have but one obstacle, the tough cuticular wall, to overcome, are often the

cause of devastating epidemics among insects. We may call to mind the losses that were formerly occasioned by the 'muscardine' of the silkworm. The epidemic disease caused by the *Isaria destructor* affects several species of beetles, especially *Cleonus punctiventris*. It often happens that more than half these insects

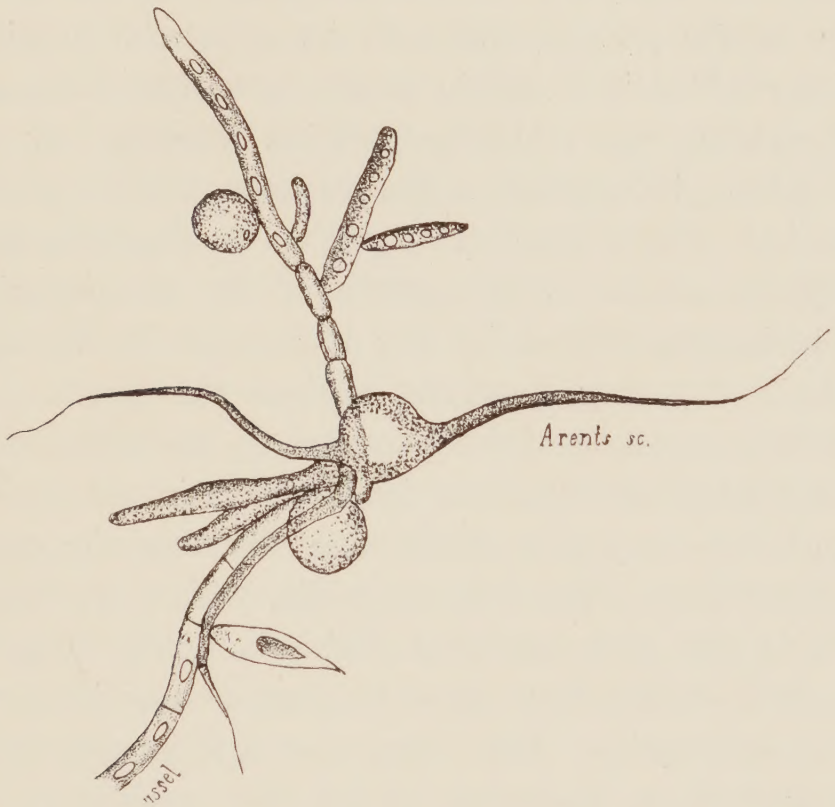

Fig. 45.—Free conidia of *Isaria* in very close promimity to some leucocytes of *Cleonus*.

perish from the attacks of the parasite. These insects do a large amount of damage to the beetroot, and the owners of the beet plantations in south-west Russia make their calculations as to the amount of seed that it will be necessary to sow, according to the rate of mortality among these insects caused by the "muscardine verte." In fact it is now a rooted conviction that the culture of beetroot in the district mentioned would be

impossible were it not for the assistance afforded naturally by the *Isaria destructor*.

The diseases of insects occasioned by Sporozoa, (a well-known example being the *pébrine* of silkworms,) have not yet been studied from the standpoint of the comparative pathology of inflammation. We are acquainted with the microsporidium[1] which is the cause of the *pébrine*, and with its amœboid condition which enables it to attain access to various cells, such as the young eggs ; but the question whether any contest takes place between the parasite and the phagocytes has not yet been investigated. In Daphnia, which is equally subject to the attack of the microsporidia, the resistance offered by the leucocytes is extremely feeble, and is only displayed against the spores. The amœboid condition of the parasites is developed in the close neighbourhood of the leucocytes, without exciting them to take any part whatever in checking the course of the disease. The microsporidia, which develop so freely in the body cavity of Daphnia, finally invading the entire animal, have absolutely no destructive action on the leucocytes. The latter circulate in the blood, now and then fastening on to the surface of the parasites and dropping off again as if they had to do with some harmless object.

In reviewing this chapter on the reactive phenomena presented by the invertebrata that are provided with amœboid and phagocytic blood-corpuscles, we are bound to conclude that in all these animals an agglomeration of these cells is produced round any injured spots. This inflammatory reaction takes place as a result

[1] See especially Balbiani, "Leçons sur les Sporozoaires," 1884, p. 150, *et seq*.

of any sort of traumatism (cauterisation, introduction of splinters, bites, &c.). It is seen also in the course of certain infectious diseases, as for example that caused in Daphnia by the presence of Monospora. In the case where the phagocytic inflammation occurs to any considerable extent, the cell accumulation consists chiefly of the leucocytes which are brought along by the blood current and are attracted to the injured spot in virtue of their sensibility. The lacunar circulation aids the approach of the leucocytes and renders unnecessary any special arrangements for the passage of these cells, such as we find in the vertebrata.

As, however, the sensibility (chemiotactic or otherwise) of the leucocytes very frequently remains negative, highly favourable conditions then exist for the inroads of all kinds of parasites. In these cases protection against infection is chiefly provided for by the thick chitinous integument with which the animal is invested, so that we have, in the Arthropoda, a means of defence analogous to that which we have seen to be possessed by Nematoda and plants. In this type of invertebrata, however, members entirely devoid of leucocytes are extremely rare, the large majority of the Arthropoda having a more or less highly organised army of these defenders.

LECTURE VII.

Vertebrata—Amphioxus—Embryos of Axolotl—Young larvæ of Urodela—Comparison with the invertebrata—Tadpoles—Diapedesis—Migratory cells—Fixed cells—Phagocytic properties of leucocytes—Do fixed cells also functionate as phagocytes?—Transformation of leucocytes into fixed connective tissue cells—Fate of the leucocytes that do not undergo this transformation—Evolution of inflammation in the organic world.

THE last survivor of the lower vertebrates, the *Amphioxus lanceolatus*, is curiously distinguished from all its congeners so far as regards its pathology. It possesses no blood corpuscles whatever, and is only furnished with a very small number of amœboid connective tissue cells. All attempts therefore to provoke inflammatory phenomena in it have given only negative results. The application of nitrate of silver, or an incision does not excite any visible reaction. This is evidently due to the fact that Amphioxus is possessed of a very tough limiting membrane, which serves as an important means of defence to the animal. In this respect it resembles the Nematoda and other animals that are protected by their chitinous cuticles, as well as most plants.

In order to obtain reactive phenomena analogous to those which take place in most invertebrata possessing a mesoderm, we might turn our attention to the class of

fishes, where we find inflammatory processes similar to those that are known from the study of the higher animals. Since, however, the fishes are ill-adapted for investigation in the living condition, it is better to pass at once to the amphibia. In this class the larval stages serve as classical objects for researches of this nature, the caudal fins of the larvæ of Urodela (Tritons and Axolotls) and the tadpoles of Batrachians offering by far the best material for the investigation of inflammation in vertebrata.

We will first consider the Urodela, which form the lowest group of the amphibia.

In the embryo of Axolotl [1] the rudiment of the fin is completely devoid of blood-vessels and lymphatics. In addition to the epidermis, it is composed of a layer of mesodermic cells which are divided at an early stage into two varieties: fixed cells with processes which ramify like a stag's horn, and amœboid cells with large mobile processes having few or no branches. Although the fixed cells form a majority of the elements of this connective tissue, the migratory cells occur in fairly large numbers. (Fig. 46.)

The embryos of Axolotl, if freed from the egg membranes at the tenth or twelfth day of development, live readily in the aquarium, and can be used for experiments on inflammation. If in one of these embryos (previously curarised), we touch the edge of the fin with a fragment of silver nitrate, and at once wash this off with a stream of saline solution, we obtain a small limited burn ; or we may produce a small lesion of the fin, by introducing a needle charged with powered car-

[1] I have always used the white variety, since these are more convenient for researches on inflammation.

mine or indigo. By either method we kill a certain number of cells, and lay bare a part of the tissue of the fin, which takes up a certain quantity of water, so that the adjoining cells, especially the stellate cells, become altered and lose to a great extent their highly refracting appearance and their vacuoles. A short time after

Fig. 46.—Connective tissue in the fin of an Axolotl embryo.
a. Amœboid cells.

the operation we may see a certain number of migratory cells making towards the injured spot, while the epidermis folds over and covers the wound. The next day some of the amœboid cells of the connective tissue accumulate round the injured spot and englobe either the coloured granules lying in the wound or the débris of the destroyed cells (Fig. 47). In this collection of cells some are to be found in the process of

karyokinetic division. The number of mitotic figures however is too small to permit of our ascribing many of the cells assembled at the seat of injury to the division of pre-existing ones. Moreover this hypothesis is unnecessary since direct observation shows clearly that it is the mobile cells which accumulate round the lesion. The stellate connective tissue cells, which can be watched from day to day in the same animal, are entirely

Fig. 47.—Inflamed spot in an Axolotl embryo.

passive in their behaviour. The karyokinetic phenomena seen in some of them, are not more pronounced than those occurring in other parts of the fin. The blood-vessels do not take any part in the changes consequent on the injury. Although they form large trunks in the tail, they are quite absent in the fin or are present only as small tubes which have no connection with the rest of the circulation.

Here then in the embryo of a vertebrate animal we have the phenomena of reaction carried out by the mobile cells of the connective tissue alone, without any

intervention on the part of the blood-vessels or of the white blood-corpuscles. There can be no doubt that this process is analogous with the reaction which, as we have seen, is the result of lesions in the Medusæ and the larvæ of Echinoderms; in both cases there is an accumulation of the phagocytes of the connective tissue round the seat of injury.

Phenomena of the same nature may be also observed in the young larvæ of Axolotl, which have blood-vessels in their fins, as well in the larvæ of Tritons, which are also provided with capillary blood-vessels. Emigration scarcely or never occurs, owing to the early vessels of these larvæ being too minute to allow of the passage through their walls of the large leucocytes, impeded in their movements as they are by the voluminous red corpuscles. Hence arises a remarkable series of phenomena. The vessels of the fin in the vicinity of the injured spot remain passive, and do not even undergo any appreciable dilatation, while the migratory cells of the connective tissue travel towards the seat of the lesion.

As the occurrence of an inflammatory reaction in vertebra without the intervention of vessels is a fact of great importance, I will devote further attention to the same phenomenon in the young larva of *Triton tæniatus*. The edge of the caudal fin of one of these larvæ was touched with a very small crystal of nitrate of silver, and washed immediately with salt solution and then with pure water, so that the lesion was confined to a small group of epidermic and connective tissue cells. The branched cells of the connective tissue that were nearest to the injured spot, became less highly refracting and absorbed fluid, so that their protoplasm

became vacuolated, while at the same time their processes were drawn in and shortened. (Fig. 48.) Two amœboid cells in the adjoining parts of the connective tissue began to move towards the seat of injury. In a subjacent capillary loop the circulation was completely arrested. Three-quarters of an hour after the application of the

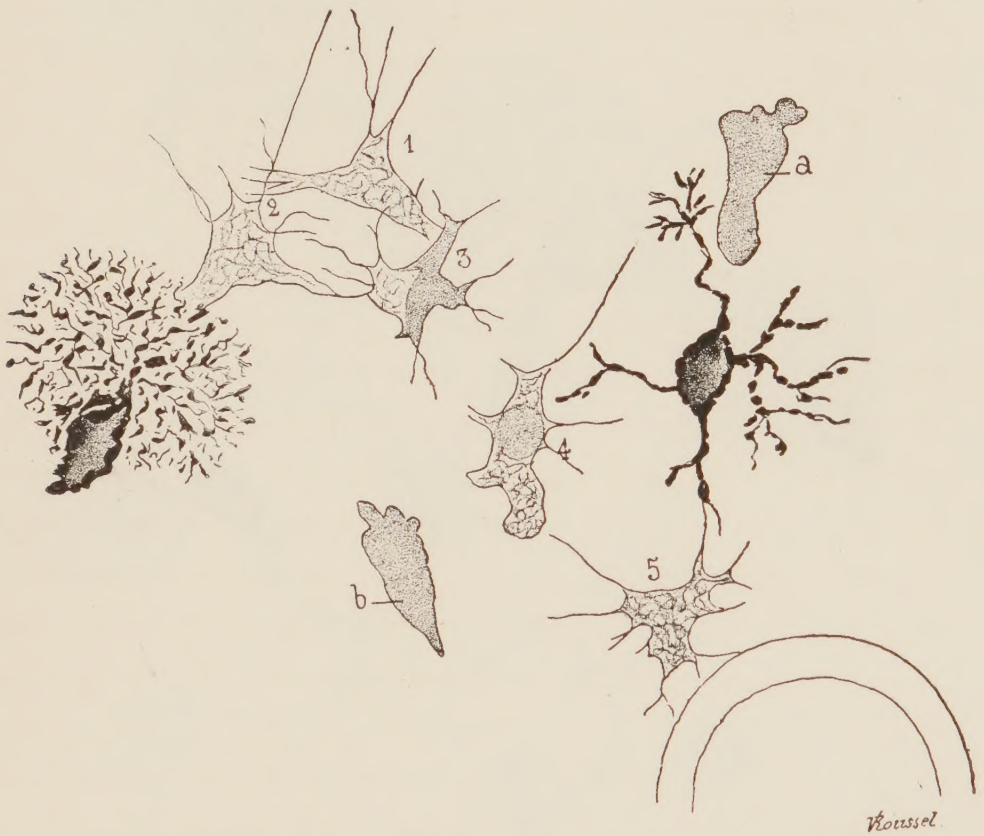

Fig. 48.—Part of the caudal fin of a Triton embryo, a quarter of an hour after the application of nitrate of silver.
1-5. Fixed connective tissue cells.—*a*, *b*. Migratory cells.

nitrate, the amœboid cells in the tissues nearest the lesion had increased somewhat in number, and all were making their way towards the cauterised spot. (Fig. 49.) Three hours after the beginning of the experiment the branched cells still retained their relative positions, but had regained their normal refractive power, and hardly showed any change in the shape of even their finest ramifications. The migratory cells continued to increase in

number, but solely at the expense of the neighbouring connective tissue, since in all the vessels the circulation appeared to have resumed its normal course, and no trace of diapedesis was to be seen. Two hours later i.e. five hours after the cauterisation), the eschar formed by the necrosed epidermis came away, disclosing a new

Fig. 49.—The same specimen, three-quarters of an hour after cauterisation. 1-5. Fixed cells.—*a*, *b*, *c*. Migratory cells.

epidermic layer, beneath which lay a mass of migratory cells. (Fig. 50.) Other mobile cells were proceeding in the same direction, whereas the fixed connective tissue cells retained their former positions. The circulation was restored in the neighbouring vascular loop and yet, as throughout the experiment, there was absolutely no diapedesis. On the following day the injured part was completely restored to a normal condition.

The stellate cells (Fig. 51) had resumed their wonted

Fig. 50.—The same spot five hours after cauterisati
1-5. The same fixed cells as in Fig. 47 and 48.

appearance and again presented their characteristic antler-like processes. The migratory cells, of which a certain number remained accumulated under the re-

generated epidermis, were as sparsely scattered in the connective tissue as in a normal animal.

On seeing how quickly this restitution took place, I again cauterised the same spot, twenty-four hours after the first experiment, with nitrate of silver but more

Fig. 51.—The same spot 24 hours after the cauterisation.
1-5. The same fixed cells as in Fig. 47-49.

severely than on the former occasion. Directly afterwards the stationary cells underwent the same changes as before; they became larger, vacuolated, and less refractive, while their processes were considerably shortened. The circulation in several adjoining capillary loops was arrested; but, in spite of the severity of the lesion, diapedesis only occurred to an insignificant degree. During five hours of observation, I saw only a

single leucocyte pass through the capillary walls. This fact however did not hinder the accumulation of migratory cells, a certain number of which made their way towards the seat of injury.

These observations, which have been repeated for several years with uniform results, demonstrate clearly the possibility of an inflammatory reaction in vertebrata, without the intervention of the vascular or nervous system. These phenomena may therefore be classed with the reactive processes in the Annelida.

Thus a genealogical tree of inflammation can be drawn up, starting with the researches on the reactive phenomena of the invertebrata, and completed by facts observed in the embryonic and early larval stages of the vertebrata. These facts prove that the reactive phenomena ensuing on lesions are in their origin essentially the same in the two great branches of the animal kingdom. But, whereas in the invertebrata the processes have remained stationary, in the vertebrata they have become in the course of development much more complex in character. Even in the older larvæ of Triton and Axolotl, which are provided with a larger number of blood-vessels wide enough to allow the passage of leucocytes, the inflammatory reaction takes place in the classical manner that has been so frequently studied during the last twenty-four years. The same lesions still produce first an acceleration, then a slowing of the blood-stream, followed by an accumulation of white corpuscles in the peripheral zone and their emigration and movement towards the injured spot.

The tadpoles of the different Batrachians are well adapted for the investigation of these phenomena; some, such as those of *Bombinator igneus*, are distin-

guished by their large fins, which are so transparent as to admit of direct microscopic examination. If inflammation be excited in the living tadpole by the application of small fragments of silver nitrate, by a simple puncture or by any other means, all the stages of inflammation and regeneration can be followed under the microscope for several days or weeks in succession. Hence the great advantage of these researches over those prosecuted on the mesentery or tongue of the frog. If we wish to fix any stage, we have only to adopt Ranvier's method,[1] and drop the whole animal into 25 per cent. alcohol. After it has been for a few hours in this liquid, the epidermis may be detached by means of forceps, the tail cut off and covered with a few drops of an aqueous solution of vesuvine. After some minutes the preparation is sufficiently stained, and may be washed with water and examined just as it is, without being dehydrated and mounted in balsam.

The tail of tadpoles shows marked anatomical differences compared with the fin of young larvæ of Triton or Axolotl. In the former the blood-vessels are much more numerous and more richly branched, while the amœboid cells normally present in the connective tissue are much less numerous. All the histological elements, the cells of the connective tissue as well as the red and white blood-corpuscles, are smaller. These peculiarities in the tadpole favour the emigration of leucocytes, which is very pronounced after the infliction of the various lesions that I have practised, such as section of the end of the tail, puncture by a foreign body or cauterisation with nitrate of silver. Sometimes, as soon as a quarter of an hour after the infliction of the

[1] "Traité technique d'histologie," 2e édition, 1889.

injury, we may see the beginning of inflammation, accompanied by vascular dilatation and a considerable emigration of leucocytes. In cases where the irritation is more lasting, as after the introduction of a splinter, the inflammatory emigration may be observed for several days in succession. The result is an accumulation of leucocytes round the seat of lesion, an accumulation infinitely more extensive than that which occurs in the young larvæ of Triton and Axolotl. A comparison of the reactive phenomena in these Urodela with those in tadpoles of Batrachians demonstrates in the clearest manner possible how much more marked the reaction becomes when the vascular system co-operates.

It is very probable that the migratory cells of the connective tissue also move towards the injured spot. Their number, however, is so limited that they are quite unimportant in comparison with the mass of emigrated leucocytes. The fixed connective tissue cells undergo the same changes that have been described in the case of the Tritons. Immediately after the application of the irritant, they swell up, become vacuolated and less highly refracting, while their processes become shorter and lose many of their branches. A short time later, however, these cells resume their normal condition, including their stationary position and other characteristics.

The migratory cells which have collected round the lesion in the young Urodela, as well as the numerous leucocytes which have emigrated from the blood-vessels in the tadpoles and in the older larvæ of the same Urodela, at once show marked phagocytic properties. They greedily devour coloured granules which have been either introduced on a foreign body

or simply rubbed into the wound ; they also englobe granules of dead pigment-corpuscles or other cellular *débris*.

In my first paper on inflammation in amphibia [1] I laid stress on the fact that the fixed ramified cells of the connective tissue are also possessed of phagocytic properties. On examining fins which have been inflamed for several days we may readily observe cells containing foreign bodies, such as granules of carmine or broken-down red corpuscles, in their protoplasm, although these cells have antler-like ramifications and must therefore be regarded as characteristic connective tissue cells. From these facts, which I have confirmed several times, I concluded that these cells were phagocytes, just as much as the migratory cells. But I have since recognised that this deduction was erroneous. In spite of numerous attempts, I have never succeeded in observing the inclusion of foreign bodies by the protoplasmic processes of the connective tissue cells. My researches on this point, which I have repeated for several years, have convinced me that the fixed cells, once definitely formed, never under any circumstances englobe granules of carmine or other substances. The granules found enclosed in them have been taken up in a previous stage of their development, when they were still mobile phagocytes. These facts afford therefore certain proof of the conversion of migratory cells into fixed connective tissue cells. Although this conclusion is opposed to the almost unanimous opinion of pathologists, it is nevertheless correct.

It does not, however, necessarily follow that all the mobile cells which have collected at the seat of lesion

[1] *Biologisches Centralblatt*, 1883.

are transformed into fixed branched cells. A great number of phagocytes do not undergo this change; many of them perish and are englobed by other phagocytes, as can be seen in every case a few days after the onset of the inflammation (Fig. 52). Several of these wandering cells penetrate into the epidermis, and escape thence to the surface, where they meet a certain death in the surrounding water. Others again pass into the lymphatics (Pl. I. Fig. 1) and are carried away by the lymph-stream. A certain number of phagocytes remain at the seat of the lesion, in spite of the fact that complete regeneration may have occurred. In the cases where the irritant remains in the tissue, as for instance the small glass tube which has been introduced into the connective tissue of tadpoles, a number of the emigrated leucocytes remain at the injured spot, sometimes surrounding the foreign body for several months.

Fig. 52.—Phagocytes enclosing other phagocytes. From the fin of a tadpole of *Bombinator*.

This description of inflammation in the tadpole may be taken as a type of the same process in the other Vertebrates, including mammals and man himself.

We have thus arrived at the final complication of the inflammatory reaction as it occurs in the animal kingdom. Before examining this pathological process in detail, it would be advantageous to cast a look back on the evolution of this important phenomenon.

Since the chief cause of inflammation—infection—

must be considered as a struggle between two organisms, the parasite and its host, and since this struggle brings about adaptations on both sides, we must admit that the organism has elaborated means to defend itself against its aggressors. If the unicellular beings, in which the nature of the struggle is more evident, already possess means of defence, we certainly cannot suppose that the higher animals are deprived of equal powers.

The plants, which are incapable of motion, defend themselves by the secretion of thick tough membranes, to penetrate which the parasite has to adopt special measures. Thus it must either secrete ferments which dissolve the cellulose, or pierce the membrane by the force of its growth, so that the plant is well defended against a large number of parasites which are not possessed of these powers.

The penetration of parasites into, or the action of any other injurious agents upon vegetable cells causes their death. But even if these cells are incapable of regeneration, others, which remain intact or are even excited by the irritant, multiply and take their place. In the plant world, then, we have lesions and primary necrosis; regeneration also takes place, often to full reintegration, but there is no such thing as inflammation.

The animal condition of some lower plants, especially the plasmodium of Myxomycetes, offers an exception to this rule, since here we have a vegetable organism capable of locomotion and cellular digestion. The latter property, which consists in taking up and digesting or excreting the deleterious matter, contributes to the protection of the organism. Although it may not constitute inflammation itself, at any rate it represents a primitive condition of this process.

Inflammation makes its appearance only in the animal kingdom and undergoes a slow evolution, which begins in the organisms that have a mesoderm. At first it cannot be distinguished from a simple intracellular digestion, effected by amœboid and phagocytic cells of the mesoderm. Thus in the Sponges the digestive and the inflammatory functions are still united; but as soon as the endoderm becomes definitely separated from the mesoderm, the two functions diverge. The endoderm now acts exclusively as a digestive organ, while the mesoderm alone retains the power of protecting the organism against injurious agents by digesting them when possible. The mesodermic phagocytes preserve their property of intracellular digestion; this they effect either by fusing into plasmodia or by collecting to form capsules round the parasites or other foreign bodies. The phagocytic reaction is displayed by all the mesodermic phagocytes. In this process the prominent part is played in some cases by the connective tissue cells, in others by the peritoneal cells or by the corpuscles of the perivisceral fluid or of the blood. In all these cases it is the phagocytes which war against the aggressor by devouring, englobing and digesting it.

It is apparent that the inflammation of vertebrates, in which the defending phagocytes emigrate from the vessels to proceed against offending bodies, is distinguished only quantitatively from the analogous phenomena in invertebrates and must therefore be also regarded as a reaction of the organism against deleterious agents. We must conclude that the essential originating factor, *the primum movens of inflammation consists in a phagocytic reaction on the part of the*

animal organism. All the other phenomena are merely accessory to this process, and may be regarded as means to facilitate the access of phagocytes to the injured part.

The morbid phenomena properly speaking, such as the primary lesion or necrosis, as well as the processes of repair, do not form part of the inflammation and must not be confounded with it.

The discussion as to which stage in the evolution of the phagocytic reaction should have the name of *inflammation* applied to it, is really beside the point. We might follow Stricker,[1] Roser,[2] and others, in limiting this term to the phenomena in which the vessels co-operate. In this case the phagocytic reaction of the older larvæ of Urodela would fall under the head of inflammation, while the same reaction in younger larvæ, where the phagocytes are furnished by the connective tissue, would have no right to this term. If on the other hand we wish to adhere to the etymological meaning of the word, we can only apply the name of 'inflammation' to those cases where the phagocytic reaction is accompanied by increased local temperature, that is to say, we must reserve it exclusively for the warm-blooded animals. The important points, with which we are concerned, are the recognition of the natural relations between the phenomena and the tracing of their genealogical history.

This general conclusion, to which we have been led by a comparative survey of the phagocytic reaction, will, I think, facilitate a closer study of inflammation in the vertebrata.

[1] "Allgemeine Pathologie der Infectionskrankheiten." Wien, 1886, p. 112.

[2] "Entzündung und Heilung." Leipzig, 1886, p. 55.

LECTURE VIII.

Varieties of leucocytes—Origin of these varieties—Mobility—Phagocytic properties—Condition of englobed microbes—Their vitality and virulence—Sensibility of leucocytes—Tactile sensibility—Chemiotaxis—Buchner's investigations—Leucocytosis—Intracellular digestion—Destruction of microbes, especially in immune animals—Action of leucocytes on spores—Multiplication of leucocytes by direct and indirect cell-division—Changes they undergo—Transformation of lobed into single nuclei.

FOR the purpose of simplification, I propose to treat the various parts of the inflammatory reaction in vertebrates separately, beginning with a study of the principal actors in this process—the leucocytes.

Of these cells, which include the colourless corpuscles contained in the blood and lymph, several varieties may be distinguished. In the first place, we find small leucocytes with a large round nucleus and a very small amount of protoplasm forming a thin layer round the nucleus. These cells (Fig. 53*a*) which are often spoken of as *lymphocytes* because they occur in large quantities in the lymphatic glands, stain readily with a variety of colours, especially with the aniline dyes. The latter stain the nucleus deeply, and the protoplasm only faintly. The lymphocytes gradually grow until they become large-sized leucocytes, provided with a single nucleus, which contains a considerable proportion of

nucleoplasm and is easily stained with the aniline colours. The nucleus of these large leucocytes, however, does not stain so deeply, whereas their protoplasm stains as well as or better than that of the lymphocytes. Among these *mononuclear leucocytes* are some cells with a round or oval nucleus (Fig. 53*b*) and others with a kidney- or bean-shaped nucleus. This kind of leucocyte bears a great resemblance to certain fixed connective tissue cells as well as to endothelial cells and cells of the splenic pulp. On this account it is often difficult to distinguish the mononuclear leucocytes from these cells, especially when they occur outside the vessels.

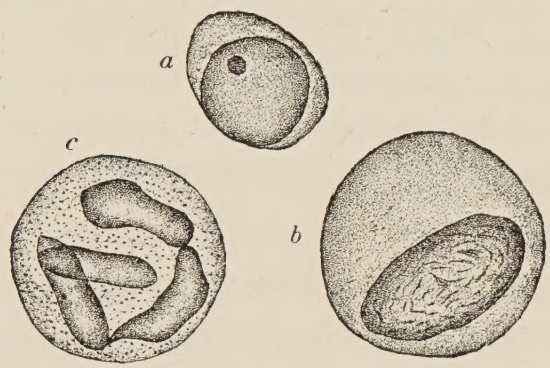

Fig. 53.—Three forms of leucocytes.

The two next varieties of leucocytes on the other hand may easily be recognised, even when surrounded with all sorts of histological elements. The first of these, the *eosinophile leucocytes* of Ehrlich, are provided with a nucleus, generally lobed and of very variable form. They contain in their protoplasm coarse granules which do not stain with the basic aniline dyes, such as fuchsine, methyl or gentian violet, methylene blue, vesuvine and others, but readily take up the acid aniline colours, especially eosin, which stains them a rose-red. (Plate III. Fig. 2.)

The fourth variety of leucocytes, the most important quantitatively and even qualitatively, is represented by cells in which the nucleus is either lobed or composed of several portions united by such delicate nuclear fila-

ments (Fig. 53*c*) as to give the impression of a multinucleated cell. Most of the nuclei are in this form, although they are sometimes really multiple, thus justifying the name of *polynuclear leucocytes*, which has been given to this kind. The shapes of these compound nuclei are very variable. They more frequently resemble a trefoil or a raspberry, but they may occur in the form of a ring. Besides the nucleus these leucocytes possess an attraction-sphere composed of fine filaments of achromatin and containing a small central body of chromatin. This peculiarity has been lately discovered by Flemming[1] in the leucocytes of salamander larvæ. (Plate II. Fig. 7.)

The polynuclear leucocytes differ from the other colourless corpuscles in their reaction to aniline dyes, which stain the nuclei very deeply, while the protoplasm remains for the most part unaffected. The latter contains granules, sometimes, as in man, in great number. These can only be stained by a mixture of the acid with the basic dyes, so that these polynuclear leucocytes are often alluded to as *neutrophile* leucocytes.[2]

Although the fact that there are several kinds of leucocytes was shown by Max Schultze[3] as long ago as 1865, an exact knowledge of the different forms dates only from the discoveries of Ehrlich.[4] On examining the relative proportion of the various leucocytes in the blood,

[1] *Archiv für mikroskop. Anatomie*, 1891, vol. xxxvii. p. 249. Plates 13 and 14.

[2] In the rabbit and guinea-pig these cells are replaced by *amphophile* or *pseudoeosinophile* leucocytes.

[3] *Archiv f. mikroskop. Anatomie*, 1865, vol. i.

[4] The valuable papers of Ehrlich have been recently collected in a single volume. "Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes." Berlin, 1891.

it is found that the neutrophile cells are by far the most numerous, forming three-fourths of the total amount.

It was at first thought that these varieties depended on a difference in the origin of the leucocytes and that the small cells were formed only in the lymphatic glands, while the others were derived from the bone-marrow. Leucocytes were accordingly divided into two groups, *lymphocytes* and *myelocytes*. This classification had to be abandoned for two reasons. In the first place, small cells can also be formed in other organs, such as the spleen and the bone-marrow; and, in the second place, the myelocytes do not originate solely in the bone-marrow. Here again our most accurate knowledge is due to Ehrlich, who has shown that the eosinophile cells are produced specially by the bone-marrow; hence an abnormal number of these cells in the blood serves to indicate that this tissue is primarily affected, as in myelogenic leuchæmia. The ordinary polynuclear leucocytes or neutrophile cells develop in the blood itself at the expense of the small cells which have been formed in various organs. This fact has been specially pointed out by Ouskoff.[1]

In considering this question of the origin of leucocytes, it must not be forgotten that these cells are to be found in the blood of the inferior fishes, such as Cyclostomata, which possess neither lymphatic glands, bone-marrow nor spleen, and in which the leucocytes are derived from the mesodermic cells of the embryo and perhaps also from the endothelium of the blood-vessels.

The leucocytes, as Lieberkühn showed, are mobile cells which, like the amœbæ, have the power of putting

[1] "Le sang comme tissu," (Russian), St. Petersburg, 1890.

out protoplasmic processes and of moving from place to place. All the leucocytes have this property; but it is not so well developed in the lymphocytes, which are the youngest of the white blood-corpuscles. Neither these nor the eosinophile cells are able to englobe foreign bodies, and therefore cannot act as phagocytes. Hence it is probable that the granules, which are so characteristic of the eosinophile cells and in reptiles and birds are shaped like small rods or crystals, are not taken up by the cells, but are manufactured in the body of the cell itself. On the other hand the two remaining varieties of leucocytes, the mononuclear and the neutrophile corpuscles are endowed with very pronounced phagocytic properties. Even outside the organism these amœboid cells readily englobe a large number of foreign particles with which they may come in contact, and they may be often seen literally crammed with all sorts of granules. Like the amœbæ, they swallow not only inert bodies, such as granules of carmine or other substances that are insoluble in the fluid surrounding the leucocytes, but also a large number of living organisms. Thus the leucocytes of the frog englobe the bacilli which cause a septicæmia in these Batrachians. That the bacilli are in a living condition when swallowed, is shown by the fact that they perform active movements although enclosed in the nutritive vacuoles of the leucocytes.[1] The same thing is observed if we introduce leucocytes filled with bacteria into a medium which nourishes the bacilli while killing the leucocyte. Thus on introducing the leucocytes of the pigeon filled with anthrax bacilli (to which the pigeon is very refractory) into bouillon, the

[1] Vide *Biologisches Centralblatt*, 1883, p. 562.

bacilli grow, pierce the protoplasm of the cells, and form well-developed filaments,[1] showing definitely that the bacilli were englobed in a living condition. This has also been proved in the case of other bacteria. Thus the *Vibrio Metchnikowii* that has been taken up by the leucocytes of immune guinea-pigs, will develop, even in an exsudation obtained from the animal itself, if the fluid be put under conditions unfavourable to the life of the animal cells.[2] The conclusion is further confirmed by the fact that masses of bacilli of tuberculosis, of swine septicæmia ('rouget des porcs') and of mouse septicæmia are englobed by the leucocytes of a large variety of animals whether susceptible or refractory to these diseases.

But although it may be clearly shown that the leucocytes enclose living microbes, we must not conclude that these cells devour all microbes indiscriminately. Thus in many cases we find that the leucocytes of an animal which is very susceptible to a certain kind of bacteria, do not take up these bacteria at all, even though they may be in contact with them. As an example we may quote the behaviour of the leucocytes of mice and guinea-pigs towards the bacilli of anthrax, or that of the leucocytes of pigeons and rabbits towards the bacteria of chicken cholera, or of the leucocytes of guinea-pigs that are susceptible to vibrionic septicæmia when brought in contact with the exciting agent of this disease.

It is evident then that leucocytes can englobe virulent microbes. This fact may be shown in another way. The two kinds of leucocytes which are phago-

[1] *Annales de l'Institut Pasteur*, 1890, p. 80.

[2] *Ibid.*, 1891, p. 471.

cytic in their action, the large mononuclear and the neutrophile leucocytes, vary in their behaviour towards different species of microbes. Thus in man the mononuclear leucocytes do not take up either the streptococcus of erysipelas or the gonococci, whereas these two microorganisms are readily englobed by the neutrophile polynuclear leucocytes.[1] This choice shows that the microbes thus avoided by the mononuclear leucocytes, are by no means inactive bodies, otherwise they would be taken up by this variety of leucocytes, just like any other inert matter. Leprosy bacilli, on the other hand, are never englobed by the neutrophile polynuclear leucocytes, but are readily devoured by the mononuclear cells.[2]

These differences must be due to a varying sensibility to microbes on the part of the two kinds of leucocytes, dependent no doubt in both instances on chemiotaxis.

Some researches on phagocytosis in amœboid cells[3] suggested that action at a distance must play some part in these phenomena. We owe to Leber,[4] however, the first clear exposition of the part taken in them by the chemiotactic sensibility of the leucocytes. In his experiments on keratitis produced by a crystalline

[1] *Virchow's Archiv*, vol. cvii., 1887, p. 227.

[2] *Ibid.*, p. 228, and Sawtchenko, *Ziegler's Beiträge zur pathologischen Anatomie*, vol. ix., 1890, p. 252.

[3] "Untersuchungen über die intracelluläre Verdauung," in the *Arbeiten des zool. Inst. zu Wien*, 1883, vol. v. p. 159.

[4] *Fortschritte der Medicin*, vol. vi., 1888, p. 460. See also Leber's large work, "Die Entstehung der Entzündung," published at Leipzig in May, 1891. As my manuscript was already written when this monograph appeared, I have not been able to quote from it so often as I should have liked.

substance extracted from cultures of *Staphylococcus aureus*, he showed that the leucocytes at a distance were attracted towards the point where this substance had been introduced. On putting some small glass tubes filled with this substance, into the anterior chamber of the eye, they became filled with a mass of leucocytes, although the tubes were so placed that the cells had to move against gravity in order to effect an entry into them.

This important discovery was the starting-point of a series of researches which proved beyond question the existence in leucocytes of chemiotactic properties absolutely analogous to those of plasmodia and other lower organisms. Lubarsch[1] showed that the leucocytes of the frog are more readily attracted by living bacilli than by the same bacilli if previously killed by heating. Pekelharing[2] then pointed out that the leucocytes of this animal are much more strongly attracted by the bacilli of anthrax than by a passive substance such as cotton fibres. In this connection many facts of great importance have been brought forward by Massart and Bordet,[3] who proved that the leucocytes of the frog are attracted by a number of culture fluids of various microbes, especially of the *Staphylococcus pyogenes albus*, as well as by the pleuroperitoneal transsudation of frogs that have been poisoned by ox-bile.

Among the products of the oxidation of albumen,

[1] *Fortschritte d. Medicin*, 1888, vol. vi. No. 4, and *Centralblatt für Bacteriologie*, vol. vi. Nos. 18-20.

[2] *Semaine médicale*, No. 22, 1889, p. 184.

[3] "Recherches sur l'irritabilité des leucocytes." *Journ. publ. par la Soc. des Sci. méd. et nat. de Bruxelles*, Feb. 3rd, 1890.

examined by these authors, leucin was the only one found to exercise an attractive influence on the frog's leucocytes, while others such as creatin, creatinin, allantoin &c., did not give rise to any chemiotaxis.

Gabritchevsky,[1] in a research carried out in my laboratory, has shown that the leucocytes of mammals, especially of the rabbit, are much more sensitive to chemical excitation than are those of the frog. He pointed out moreover that whereas leucocytes are strongly attracted by sterilised or living cultures of most pathogenic and saprophytic bacteria as well as by papayotin, they are repelled by the most virulent bacteria, such as those of chicken cholera, and by lactic acid, ten per cent. solutions of sodium and potassium salts, alcohol, chloroform, glycerine, jequirity, bile and quinine. The leucocytes remain unaffected by many other substances such as water, weak solutions of sodium or potassium salts, peptone, phloridzin, &c.

Buchner,[2] after confirming these facts on the chemiotactic properties of leucocytes, has endeavoured to determine more precisely the nature of the substances contained in bacterial cultivations which call these properties into play. In conjunction with Lange and Römer he found that the proteins of various species (*bacillus pyocyaneus*, *bacillus subtilis*, the typhoid bacillus, *Staphylococcus pyogenes aureus* and others) exercised an attractive influence on the leucocytes of the rabbit. He obtained the same effect with solutions of gluten-casein, as well as with some alkali-albumens of animal origin. Buchner considers that these experiments warrant the conclusion that it is only the contents of bacteria, and

[1] *Annales de l'Institut Pasteur*, 1890, p. 346.

[2] *Berliner klinische Wochenschrift*, 1890, No. 47.

not the products of their secretion, which exert a chemiotactic influence on the leucocytes. We must observe, however, that Buchner has not by any means proved his contention. It is evident that the toxic products of the bacteria must play the most important part in evoking the phenomena of chemiotaxis. Now it is precisely these products which adhere most strongly to albuminoid and other bodies, so that we are still far from being able to isolate them and study their effects in a pure condition. On the other hand, the more advanced products of disintegration, such as ammonia and its salts, are not of such great importance in the question of leucocytic sensibility in the animal body as to permit of our drawing conclusions from the fact that they exert no chemiotactic influence. And yet, even among these substances, we find a body, leucin, which has the property of attracting leucocytes. This fact was observed by Massart and Bordet, and has been confirmed by Buchner himself.

Physiological chemistry is not yet sufficiently advanced to give a decision in the question raised by Buchner. We have not sufficient evidence therefore to justify us in accepting the dictum laid down by this author, viz. that the chemiotaxis of leucocytes can only be excited by dead or injured bacteria, since only under such conditions are their contents dissolved out into the surrounding fluid. Even if Buchner's hypothesis could be proved, we must remember that in every medium tenanted by bacteria, there are a certain number of dead ones among the living. The former would attract the leucocytes, which would thus be brought in contact with the living bacteria, and the final result would be the same as if the living bacteria had them-

selves exercised the chemiotactic influence. But besides these considerations, there are other facts which tell against this hypothesis, as, for instance, the greater attractive power possessed by living bacteria on leucocytes, as shown in the experiments of Lubarsch. Further there are the still more important cases in which the bacteria or other parasites have been englobed by the leucocytes in the living condition. Moreover the evidence brought forward by Buchner himself argues against his idea that the leucocytes are not attracted by active bacteria. In experiments made in conjunction with Römer, Buchner found that injections of proteins of bacteria, especially of the *bacillus pyocyaneus*, into a vein, produced a pronounced general leucocytosis, the number of white corpuscles in the blood being seven times the normal amount. Now leucocytosis is a condition of extremely frequent occurrence in the infectious diseases generally. Although in some, such as typhoid fever in man, the number of leucocytes has not always been observed to be increased, yet in the vast majority of the other infectious disorders this has been found to be the case. Thus several observers [1] have shown that a pronounced leucocytosis accompanies infection by anthrax in animals which die of this disease (such as guinea-pigs, horses, oxen and others), although masses of actively living bacteria occur at the same time in the blood.

According to von Limbeck [2] and Pée,[3] leucocytosis

[1] Bollinger, "Milzbrand," 1872, pp. 2, 101.

[2] Von Limbeck, "Klinisches und Experimentelles über die entzündliche Leucocytose," Prag, 1889.

[3] H. Pée, "Untersuchungen über Leucocytose," Berlin, 1890, p. 13.

is a constant phenomenon in erysipelas in man. It is at its height during the febrile period, while the blood contains a number of living streptococci, and comes to an end after the crisis, when only masses of dead microbes are to be found in the organism.

This coincidence in time of the leucocytosis and the most active condition of the bacteria has been also shown by von Limbeck in the case of fibrinous pneumonia in man. The number of the colourless corpuscles present at any time in the blood corresponds exactly with the temperature; when the disease terminates in crisis, the leucocytes decrease suddenly, while in the cases where the temperature drops slowly, (lysis), the fall in the number of leucocytes is also gradual.

Working with dogs, von Limbeck pointed out that the injection of *Staphylococcus pyogenes aureus* into the knee-joint was almost immediately followed by a large increase of the leucocytes in the blood, before any local symptoms had made their appearance.

We thus see that the special instance of chemiotaxis known as leucocytosis, occurs at a time when the greatest proliferation of microbes is taking place and that the leucocytosis begins to diminish directly the pathogenic bacteria die. We must remember also that, according to other researches of Buchner,[1] these same proteins, which he considers to exist exclusively in the interior of the bacterial cell, are the active agents in producing fever, that is, the symptom which occurs while the pathogenic microbes are actively multiplying, and ceases with their death.

Like the plasmodium of Myxomycetes and many other

[1] *Berliner klinische Wochenschrift*, 1890, No. 30, p. 673.

inferior organisms, the leucocytes have other forms of sensibility besides that of chemiotaxis. Their tactile sensibility, which serves them in the inclusion of foreign bodies, is very highly developed. When the leucocytes meet a resistant surface, they react by offering as large a surface of contact as possible (Massart and Bordet). By means of this property, the leucocytes are able to get through the finest pores, and can penetrate elder-pith and even such compact bodies as bone and ivory. The physical changes in the surrounding medium, such as variations in temperature, pressure, or rapidity of movement of the liquid, and probably many others, must be appreciated by the leucocytes. It would be very interesting to make a systematic study of these physiotactic properties of the white corpuscles.

Leucocytes which, by virtue of their chemiotaxis, are attracted at a distance by microbes and other particles, move towards these bodies and on coming in contact with them englobe them owing to their tactile sensibility. The ingested particles are now acted on by the leucocyte. It is an old observation that red corpuscles, when enclosed by leucocytes, partially dissolve, leaving a pigmented residue. It is also very easy to follow the changes undergone by pus-corpuscles in the interior of leucocytes, where they gradually lose their staining power and are finally converted into scattered granules which are partially dissolved. These changes are carried out by the protoplasm of the leucocytes, and must be looked upon as an act of intracellular digestion. This view is justified by the discovery of ferments in leucocytes. Thus Rossbach [1] has

[1] *Deutsche medecin. Wochenschrift*, 1890, p. 389.

shown the existence of an amylolytic ferment in leucocytes from various organs, especially from the tonsils, and Leber [1] has proved that the pus from a hypopion, entirely freed from microbes, will digest coagulated fibrin at a temperature of 25°. The same pus has also the power of liquefying gelatin. This digestive power can be destroyed by heat, showing that in this respect the ferment of the leucocytes resembles all other ferments.

The digestion of proteid substances by the leucocytes is well shown by the gradual changes that take place in the muscular fibres which have been englobed by leucocytes in cases of acute muscular atrophy. The presence of peptone in leucocytes, which has been so often proved by Hofmeister, is sufficiently accounted for by this fact of intracellular digestion and need not therefore be referred, as done by this author, to an absorption by these cells of the peptone formed in the alimentary canal.

Our knowledge of the conditions under which this intracellular digestion takes place is still very incomplete. In a large number of experiments that I have made on the absorption of granules of blue litmus by leucocytes, I have seen the colour change to red only in a few exceptional cases. [2] It appears then that diges-

[1] "Die Entstehung der Entzündung," p. 508.

[2] *Annales de l'Institut Pasteur*, 1889, p. 29. Netchaeff (*Virchow's Archiv*, vol. cxxv., 1891, p. 448) thinks that in the cases where I observed a conversion of the blue into red granules, the change was simply an optical illusion. This he concludes from his own observations on the fate of litmus granules in the interior of leucocytes. My researches, which extend over a series of years, leave me, however, in no doubt as to the reality of the change in colour of the litmus. I must add that the criticism by Netchaeff of my work

tion is carried out by leucocytes in a neutral or alkaline medium, as in the case of the phagocytes of the Sponges.

Not only are the disintegrated muscle fibres or blood corpuscles digested by the leucocytes, but in a large number of cases the microbes that have been devoured also undergo the same fate. This digestion of bacteria in the interior of leucocytes can be most readily studied in refractory animals. Nothing is more instructive to watch than the changes undergone by the streptococci of erysipelas in the leucocytes of white rats. The bacteria that have been englobed fuse into irregular masses which do not stain completely, a process closely resembling the digestion of the sulphobacteria in the body of Stentor, discussed in the second lecture. Anthrax bacilli are digested in the same way by the leucocytes of a number of immune animals. The frog's white corpuscles, instead of presenting a favourable medium for the development of anthrax bacilli as Koch [1] and Petruschky [2] have asserted, not only prevent their growth and development, but also kill and digest these bacteria. All the phases of this digestion correspond exactly with those of the digestion of the saprophytic bacilli by amœbæ (*vide* Chap. II.). As in this case, a number of the bacilli in the interior of the leucocytes are stained deeply by an old aqueous solution of vesuvine, which also colours other particles that are being digested by the amœbæ, as Bruno Hofer has

on intracellular digestion shows that this observer has never examined the most classical examples of this process, more especially the digestion in Protozoa.

[1] "Beiträge zur Biologie der Pflanzen," published by Cohn, 1876, vol. ii. p. 300.

Zeitschrift für Hygiene, 1889, vol. vii. p. 75.

also shown. This period during which the devoured bacilli are deeply stained, is followed by a stage in which the bacilli are only partially stained, and finally even this property is lost and they remain absolutely uncoloured. At last only the more durable cell-membrane of the microbe is to be seen in the leucocyte, and even this disappears at the end of a certain space of time. The bacilli which have been englobed by leucocytes are much more rapidly digested in the case of mammals that are either naturally refractory, as the dog and fowl, or have been rendered artificially immune against anthrax by vaccination, as the rabbit. This fact is shown by the researches of Hess[1] as well as my own.[2]

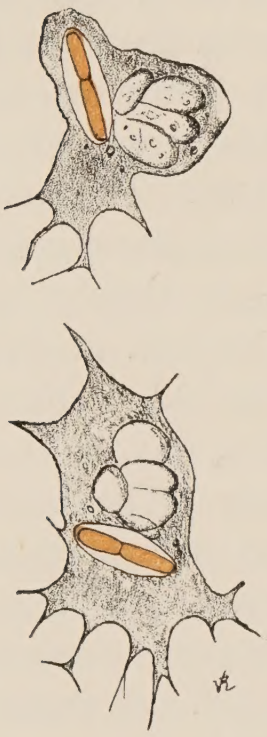

Fig. 54.—An anthrax bacillus, stained by vesuvine, in a leucocyte of the frog. The two figures represent two phases of movement of the same cell.

It is easy to follow the digestion of many other microbes within the leucocytes. Vacuoles are often seen to form around the bacteria that have been swallowed, just as we have noticed in the digestion of nutrient material by the protoplasm of the Protozoa and the Myxomycetes. I have been able to observe the changes undergone by the spirilla of recurrent fever in the leucocytes of monkeys,[3] as well as those undergone by the vibrio of septicæmia in the leucocytes of immunised guinea-pigs, and those by erysipelas streptococci in the leucocytes

[1] *Virchow's Archiv*, 1887, vol. cix. p. 365.
[2] *Ibid.*, 1884, vol. xcvii. p. 502.
[3] *Ibid.*, 1887, vol. cix. p. 176.

of man,[1] &c. We are at present ignorant of the precise manner in which this digestive and destructive action is accomplished, and do not even know whether the substance which kills the microbes is a ferment or not. The fact that the ferments of the higher animals, such as pepsin and trypsin, do not kill bacteria, is no reason

Fig. 55.—Four leucocytes from the frog, enclosing anthrax bacilli. Some are alive and unstained, others which have been killed have taken up the dye.

for assuming that there may not be other ferments which are capable of exercising a bactericidal action.

Some authors have denied to leucocytes the possession of digestive powers. Schäfer[2] comes to this conclusion from the observation that neither proteid sub-

[1] *Virchow's Archiv*, vol. cvii. p. 209.

[2] *British Medical Journal*, 1882, No. 1134, p. 573.

stances nor granules of fat or starch underwent any change when ingested by the leucocytes of Tritons. But as his researches were carried out on leucocytes that had been removed from the body and immersed in normal salt solution, they cannot be taken to refute the facts that have been acquired from a study of the living animal. Netchaeff has recently endeavoured to disprove the intracellular digestion of bacteria by leucocytes, but we have already shown how inadequate are the arguments he brings forward.

It is undeniable then that leucocytes possess digestive powers, and that in particular they are able to digest microbes. But it does not therefore necessarily follow that these cells kill and digest all the microbes they englobe. In certain diseases the leucocytes take in a number of bacteria, such as tubercle bacilli or the bacilli of swine erysipelas or mouse septicæmia, a few of which may be digested while the others resist the digestive action of the leucocytes, multiply in the cells and finally invade the whole organism.

In several cases where the leucocytes have not the power of killing the microbe, they can nevertheless hinder it from growing and exerting its toxic influence. The best examples of this are afforded by bacterial spores, which are endowed with great powers of resistance. Anthrax spores are readily ingested by the leucocytes of many species of animals, and, among others, by those of immune animals such as the frog and fowl. In spite of the fact that the spores germinate and grow easily in the lymph-plasma of the two last-mentioned, they are incapable of doing so in the bodies of the leucocytes themselves, where they cannot exert their injurious effects, although they preserve their

vitality and their virulence often for a considerable length of time. Once, however, that the vitality of these cells has been extensively lowered, as may be effected in fowls by cooling them or in frogs by heating them artificially, the spores germinate within the dead or enfeebled leucocytes, and infect the whole body.[1] These experiments were repeated several times by Trapeznikoff[2] in my laboratory, and show in a most striking manner the important and salutary part played by the leucocytes, in cases where these cells are unable to kill the spore, and where the fluids of the organism are totally inadequate to protect the infected animal.

The proliferation of leucocytes is at present the subject of much discussion. The polynuclear forms, with fragmented nucleus, can give rise to two new leucocytes by mere division of their protoplasm. This phenomenon has been described by Ranvier[3] and observed by several other workers, especially by Arnold.[4] The fact of the occurrence of simple or direct division of polynuclear leucocytes has at length been generally accepted, although for a long time after the discovery of karyokinetic or indirect cell division, it was considered doubtful, and all cells were supposed to divide in the latter way. The phenomenon of direct cell division once established, people have gone to the opposite extreme and denied to the polynuclear leucocytes the power of dividing in any other manner. All the cases in which karyokinetic division of leucocytes had been observed,

[1] See Wagner's paper on this subject, *Annales de l'Institut Pasteur*, 1890, p. 570.

[2] *Ibid.*, 1891, p. 362.

[3] "Traité d'histologie technique," 2nd edition, 1889, p. 137.

[4] *Archiv für mikroskopische Anatomie*, 1888, p. 270.

from those of Peremeschko and Koultchitsky [1] onwards, were looked upon as open to doubt. Yet it has several times been proved that leucocytes are capable of dividing indirectly. Flemming [2] has observed this phenomenon on several occasions, and has recently confirmed it in the case of the leucocytes of the salamander. Spronck,[3] too, has seen mitotic division of the leucocytes in the blood of the rabbit and has found that at any given time about 2 per 1000 of these cells are normally undergoing indirect cell-division. I can completely endorse this statement, since I have observed undoubted mitotic division of the rabbit's leucocytes in preparations made by Dr. Muskatbluth in my laboratory at Odessa. I have on several occasions noticed the same phenomenon in the migratory cells of the larvæ of Axolotl. In all the above cases it is the large mononuclear leucocytes that divide indirectly, while the polynuclear multiply by direct cell-division. All the phases of the karyokinetic division of the leucocytes that have emigrated from the vessels, and the conversion of the new cells into amœboid cells may be studied in the caudal fin of the living larvæ of the white Axolotl. (Fig. 56.)

In the same way it has been denied that the leucocytes possess the power of gradual transformation. The fact that numbers of these cells are found dead in exsudations has given rise to the idea that leucocytes are in most cases destined to perish and are incapable of forming constituent cells of any tissue. The lobed shape of the nucleus in the polynuclear leucocytes has

[1] *Centralblatt für medicinische Wissenschaften.*

[2] *Archiv für mikroskopische Anatomie*, vol. xxxvii., 1891, p. 249.

[3] *Nederlandsch Tijdscrift voor Geneeskunde*, March 29th, 1889.

even been taken as a sign of disintegration. Under the influence of these views, many authors would refuse to the leucocytes the power of conversion into fixed connective tissue cells or even into epithelioid or giant cells. In fact they now hold the exact opposite of the theory formerly maintained by Cohnheim and especially by Ziegler.[1] The latter observer at first regarded the granulation-cells as well as the epithelioid and giant cells of tubercle as derived exclusively from mononuclear leucocytes. He has now abandoned this position and

Fig. 56.—A migratory cell from the fin of a larva of Axolotl in process of division by karyokinesis.

has adopted the opinion of his former opponents, who believe the leucocyte to be incapable of giving rise to any other form of cell. At the International Congress held at Berlin in 1890, Ziegler,[2] relying chiefly on researches that had been made by Nikiforoff in his laboratory at Freiburg, stated that "the leucocytes do not take any active part in the new formation of tissues."

[1] "Ueber die pathologische Bindegewebsneubildung," 1875.

[2] *Centralblatt für allgemeine Pathologie*, 1890, Nos. 18 and 19, p 575.

Marchand[1] and Grawitz[2] quoted their own original observations in confirmation of this view. According to them the leucocytes that emigrate during an inflammation are not converted into granulation-cells, but perish in the exsudation, and are either absorbed by the lymphatics or devoured by amœboid cells derived from the fixed connective tissue cells. Ribbert[3] holds a similar opinion.

Nikiforoff's[4] experiments, on which Ziegler chiefly bases his view, were made on the subcutaneous connective tissue of dogs, in which the formation of granulation-tissue was provoked by the introduction of drainage tubes. Although he affirms that this regeneration of tissues is due exclusively to the proliferation of the tissue-cells, and that the leucocytes do not take any more active part in this process than the red corpuscles or the fibrin, yet he himself confesses he is unable to bring forward adequate proof that the "cells originating from the blood-vessels are incapable of further development and of conversion into epithelioid cells and fibroblasts."[5] Nikiforoff adds: "Judging from my observations, I am inclined to the view that in the granulation-tissue the mononuclear leucocytes are converted by fragmentation of the nuclei into polynuclear forms and are then taken up by phagocytes."[6] This sentence is certainly much less positive in tone than his conclusion quoted above and than Ziegler's dictum. If we read Nikiforoff's account of the observations themselves, we shall see that they by

[1] *Centralblatt für allgemeine Pathologie*, 1890, p. 577.

[2] *Ibid.*, p. 578. [3] *Ibid.*, p. 665.

[4] *Ziegler's Beiträge zur pathologischen Anatomie*, vol. viii., 1890, p. 400.

[5] *Ibid.*, p. 415. [6] *Ibid.*, p. 421.

no means prove his principal thesis, *i.e.* the non-participation of the leucocytes in the formation of granulation-tissue. The appearance of granulation-cells at a period when the fixed connective tissue cells are in process of multiplication, does not afford any proof that the leucocytes are not also involved. Another argument brought forward by this author, the occurrence of mitotic division, does not in the least support his conclusion, since we now know that the leucocytes are undoubtedly capable of this mode of division.

Fig. 57.—Transition stages between amœboid and fixed cells. From the tail of a tadpole of *Rana agilis*.

It is not a matter for surprise that Nikiforoff's results should be wanting in accuracy and clearness. The material he worked with, the granulations of the subcutaneous tissue in dogs, is not well adapted for the investigation of the processes under discussion. In order to obtain reliable results, we must make use of a subject on which we can follow the course of events from day to day. For instance if we take the tail of a batrachian tadpole and injure it in any way and watch it for several days or even weeks in the living condition, as I have done in my researches, it may readily be seen that in these animals the polynuclear cells are converted by a fusion of their nuclei first into mononuclear and then into typical branched connective tissue cells.

(Fig. 57.) In order to bring out this fact more clearly it is advisable to inflict the wound with an instrument

Fig. 58.—Inflamed spot of the tail of a larva of *Bombinator igneus* 8 days after cauterisation.

powdered with carmine. The granules of this substance which have been ingested by the emigrated leucocytes, are found in the interior of the connective tissue cells, the

nature of which is easily recognised by their characteristic antler-like processes. (Fig. 58.)

The view accepted at the Berlin Congress cannot be maintained. It is not the new theory of Ziegler, but his old way of thinking of 1875-1876 which is correct. Although my personal observations have only been concerned with amphibia, yet they agree perfectly with the facts that have been ascertained in the higher vertebrata by all observers, not excepting Nikiforoff himself.

In further support of my view I may quote the last communication of Flemming,[1] who has also seen the lobed or multiple nuclei of the migratory cells become fused to a single rounded nucleus in the gills of salamander larvæ.

In the mammals, however, we have no proof that the polynuclear can be transformed into mononuclear leucocytes. Although the latter do certainly become converted into epithelioid and giant cells, the polynuclear variety seems unable to be thus transformed. I need however only adduce the fact of the formation of epithelioid and giant cells at the expense of mononuclear leucocytes in the interior of the vessels in rabbits which have received an intravenous injection of tubercle bacilli. This phenomenon, which was described by Yersin,[2] has been likewise observed several times by myself.[3] Tchistowitch[4] in a research carried out in my laboratory, has also witnessed all the transition stages between typical mononuclear leuco-

[1] *Archiv f. mikroskop. Anatomie.* Vol. xxxvii., 1891, p. 277.

[2] *Annales de l'Institut Pasteur*, 1888, p. 257.

[3] *Virchow's Archiv*, July, 1888, p. 88.

[4] *Annales de l'Institut Pasteur*, July, 1889, p. 347, and Pl. vi. Figs. 5 and 7.

cytes and epithelioid and giant cells in the pulmonary alveoli of rabbits.

In summarising this review of the present state of our knowledge on the subject of leucocytes, we may conclude that the two varieties of these cells which play the principal part in inflammation—the mononuclear leucocytes and the neutrophile cells—are elements endowed with very considerable chemiotactic and physiotactic sensibilities; that they are capable of amœboid movements, and prone to englobe and digest different foreign bodies, especially a number of living microbes. In the amphibia at least, the polynuclear can be converted into mononuclear leucocytes and can become fixed connective tissue cells. In the vertebrata generally, the mononuclear leucocytes may undergo transformation into epithelioid and giant cells.

All that has been said on the subject of leucocytes refers equally to all migratory cells.

LECTURE IX.

Endothelium of vessel walls—Their development out of the mobile cells of the embryo—Development of the capillaries—Contractility of the endothelial cells—Star cells—Phagocytosis in the endothelial cells—Fixed connective tissue cells—Clasmatocytes of Ranvier—Ehrlich's cells—Active migration of leucocytes in diapedesis—Experiments with quinine (Binz, Disselhorst)—"Itio in partes"—Dilatation of the vessels—Theory invoking the influence of the surrounding tissue—Influence of the nervous system—Negative chemiotaxis of the leucocytes in cases of severe infection.

NEXT to the leucocytes, the vessels and their endothelial lining play the most important part in inflammation. According to modern embryological research on fishes[1] the first endothelial cells of the vessels are formed from the mobile cells on the surface of the yolk sac. It is therefore not a matter for wonder that the endothelial elements should have retained a few traces of their ancient power of movement. The attention of investigators has been especially directed towards the protoplasmic processes of the endothelial cells of the vessels during the new formation of capillaries. Conical buds of protoplasm make their appearance on the vascular walls. A protuberance show-

[1] *Vide* H. Ziegler, "Die Entstehung des Blutes der Wirbelthiere." Freiburg i. B., 1889.

ing very slight signs of movement thus arises and grows gradually longer. These processes often meet each other, and form loops which are at first solid and afterwards become excavated with the formation of a vascular channel. Many observers, such as Stricker,[1] Goloubew,[2] Klebs,[3] and Severini,[4] have found that the endothelial walls of capillaries are to a certain extent contractile,—a still further proof of a power of movement inherent in these cells. This property must certainly play an important part in the formation of stomata during inflammation, as Klebs[5] thought, and as I imagined and stated in my first papers on inflammation.[6] Arnold based his

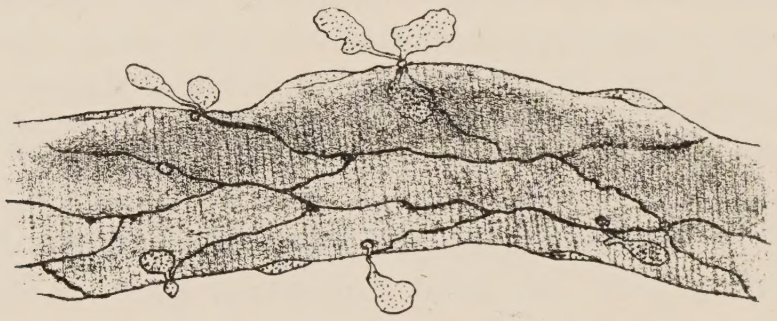

Fig. 59.—Passage of leucocytes through stigmata. (After Arnold.)

original theory of stomata on the supposed pre-existence of these orifices under normal conditions. This is not the case however, since they are formed only at the

[1] *Moleschott's Untersuchungen zur Naturlehre*, vol. x.

[2] *Archiv f. mikroskop. Anat.*, 1868.

[3] "Allgemeine Pathologie," 1889, vol. ii. p. 384.

[4] "La contrattilità dei capillari," 1881.

[5] See also Leydig, who in his pamphlet "Zelle und Gewebe," 1885, p. 17, has expressed the opinion that "in order to permit the passage of the blood corpuscles, the minute pores may often dilate into large orifices."

[6] *Biologisches Centralblatt*, 1883, p. 564.

time of the inflammatory reaction, as he himself showed [1] when he put forward his stigmata theory. (Fig. 59.) Although Arnold does not allude to the contractility of the endothelial cells, he admits that "the spaces between the cells alter according to the conditions of tension and diffusion, so that the respective positions of the endothelial cells may vary very greatly." [2] He holds that the intercellular spaces are filled with a fluid or viscous material. These pores between the endothelial cells, which open to permit of the passage of the corpuscles and liquid parts of the blood, and close after their passage, might with greater justice be compared to the pores of the ectoderm in the Sponges, which open and close on the passage of the corpuscles suspended in the surrounding water. In both cases we have to do with contractile cells whose movements may be aided by the neighbouring cells (fusiform cells of the Sponges and contractile cells of the endothelium of the vessel wall).

The contractility of the endothelial cells may be further shown by the fact that in some cases these cells may leave the vessel wall and by means of their amœboid movements wander into the lumen of the vessel. This may be observed after injection of tubercle bacilli into the circulation of rabbits. Some time after the injection has been effected, it is found that the vessel wall in some places is composed solely of the adventitia, the endothelial lining having entirely disappeared. This is very frequently found to be the case in the hepatic capillaries, where, as Eberth and others have shown, the endothelium does not present the typical

[1] *Virchow's Archiv*, 1875, vol. lxii. p. 487.

[2] *Ibid.*, 1876, vol. xlvi. p. 104.

cell boundaries on treatment with nitrate of silver. The endothelial cells of the hepatic capillaries become readily detached from the outer coat, appearing in the form of 'star-cells' provided with a number of processes which vary much in appearance. These cells, which were first described by Kupffer,[1] were originally looked upon as nervous elements on account of their shape and thin elongated processes. It was soon ascertained however that they belong to the endothelial tissue[2] and that they have the power of ingesting various granules. They are frequently found, especially in frogs, enclosing masses of reddish pigment, and they readily take up granules of pigment, if these be injected into the blood, as Ponfick[3] and others have shown.

Star-cells, in common with the other endothelial cells of the vessels, have also the power of englobing various pathogenic and saprophytic microbes which have made their way into the blood. This is the case with the leprosy bacilli, which have been found, sometimes in groups, in the endothelial cells of the blood-vessels. They often occur in such large numbers that they completely obscure the nucleus. This discovery was made by Neisser[4] and Touton,[5] who stated that certain endothelial cells, when filled with bacilli, become detached from the vessel-wall and are found free in the lumen. Wyssokowitch[6] has since found that

[1] *Archiv f. mikroskop. Anat.*, vol. xii. p. 353.

[2] Asch. "Ueber die Ablagerung von Fett und Pigment in den Sternzellen der Leber." Bonn, 1884.

[3] *Virchow's Archiv*, 1869, vol. xlviii. p. 1.

[4] Ibid., 1881, vol. lxxxiv.

[5] *Fortschritte der Medicin*, 1886, No. 2, p. 48. (*Virchow's Archiv*, 1886, vol. civ. p. 381.)

[6] *Zeitschr. f. Hygiene*, 1886, vol. i. p. 1. See also the journal *Wratch*, No. 44, 1891, p. 991.

many microbes, when injected into the circulation of rabbits, may be traced in the endothelial cells of the hepatic capillaries. This may be observed some time after the introduction of tubercle bacilli into the vein of the rabbit's ear; a large proportion of the bacilli are found again in the endothelial cells, especially in the liver. The same thing occurs in natural infections in man. Thus after death from malaria, the endothelial cells of the liver are found filled with the characteristic parasite of this disorder. Perhaps the most striking instance is furnished by pigeons that have been inoculated with the bacillus of swine septicæmia. Enormous masses of these microbes are found filling nearly the whole of the endothelial cells of the blood-vessels, especially in the liver. (Fig. 60.) As this bacillus, like that of leprosy, is non-mobile, its presence within the protoplasm of the endothelial cells can only be regarded as due to an active ingestion on the part of the cells themselves.

Fig. 60.—Endothelial cells enclosing the bacilli of swine septicæmia, from a hepatic vein of a pigeon.

I have laid weight on these details, since the contractility and the phagocytic properties of the endothelial cells are extremely important facts in the question of inflammation. Other varieties of endothelial cells are endowed with the same properties. Thus the lym-

phatic endothelial cells are still more often the seat of leprosy bacilli than those of the blood-vessels. Ranvier,[1] many years ago, showed that in the guinea-pig the endothelial cells of the inflamed omentum were capable of taking up foreign bodies (such as myelin or vermilion) that had been injected into the peritoneal cavity. In a recent study [2] of the inflammatory changes in the omentum, he has been able to demonstrate the contractility of the cells forming its endothelial covering. Moreover Ribbert,[3] in his memoir on the inflammation and regeneration of lymphatic glands, frequently lays stress on the contractility of the endothelial cells of these organs.

The connective tissue cells certainly take some part in inflammation, but this part is evidently much less important or constant than was formerly thought, and is far transcended by the part played by the leucocytes and the endothelial cells of the blood-vessels. Further we must remember that it is extremely difficult to make sure of the co-operation of connective tissue cells in the processes of inflammation. If they be studied in the tails of tadpoles or of Urodelan larvæ, the only changes that we see in the fixed connective tissue cells are alterations in their shape and their processes. These changes last only a short time, and must therefore be regarded as the immediate result of the lesion. These facts prove that an absolutely typical inflammatory reaction may occur without the fixed connective tissue cells taking any important part in the process. These cells, however, proliferate in an inflamed organ, and

[1] "Leçons sur le système nerveux," 1878, vol. i. p. 304.

[2] *Comptes rendus de l'Acad. des Sciences*, April 20, 1891, p. 842.

[3] Ziegler's *Beiträge zur pathol. Anat.*, vol. vi. 1889, p. 205.

so furnish a supply of new cells to replace those killed by the original injury. Hence at a more or less advanced stage of inflammation, karyokinetic figures are to be seen in the connective tissue cells.

Ranvier[1] has recently called attention to a variety of connective tissue cells corresponding to the "plasma cells" of Waldeyer, which he designates as *clasmatocytes*. (Pl. II., Fig. 8.) These are very large granular cells with processes and are formed from leucocytes or migratory cells, which have increased in size and lost their power of movement. During inflammation, according to Ranvier, the clasmatocytes regain their former mobility, multiply rapidly and contribute to the formation of pus-cells. On this view, the clasmatocytes would form only a temporary constituent element of the connective tissues, and would serve as a source from which leucocytes might be drawn should inflammation take place. These cells are present in large numbers in the peritoneal tissue of tritons, frogs and rabbits, but are not found in the larval stages of amphibians.

Certain other cells of the connective tissue seem to take some part in the process of inflammation. Thus the basophile cells or "Mastzellen" of Ehrlich (Pl. III., Fig. 3) are often numerously represented in the inflammatory products, although we are quite unable to explain their presence under these circumstances. Certain peculiarities in the reaction of these granules to various stains seem to point to a possibility that these cells may act as scavengers and clear away the inflammatory products. Might we not indeed look

[1] *Comptes rendus de l'Acad. des Sciences*, April 27, 1891, p. 922.

upon the granules with which they are filled as the excreta of the other cells ?

Having considered the principal cellular elements that take part in the inflammatory reaction, we may now inquire how they carry out their functions. I need not insist at length on the fact that the migration of the leucocytes through the vascular wall is due to their own active movements. In spite of all Cohnheim's endeavours, in spite of the general desire to refer all vital phenomena to mechanical causes, the view that the emigration is effected by the amœboid power of the leucocytes has now found almost unanimous acceptance (Thoma, von Recklinghausen, Lavdovsky and others). This fact must strike anyone who compares the ease with which leucocytes traverse the vascular wall, with the purely passive diapedesis of the red blood-corpuscles. The latter often remain attached for an indefinite time to the wall or are torn to pieces instead of passing outside the vessels. Even Hering[1] who originated the theory of the mechanical filtration of leucocytes at the time of inflammation, admits the participation of the amœboid movements of these cells, although not attributing any great importance to them. According to him the blood must either be circulating or be subjected to a certain pressure for the filtration of leucocytes to take place. Now the complete emigration of leucocytes may readily be observed after entire stoppage of the heart in tadpoles which have, as sometimes happens during an experiment, died from the effects of the curare administered to them. (Fig. 61.)

[1] *Sitzungsberichte der k. Akad. der Wissensch. in Wien*, 1868, vol. lvii., Part ii., p. 170.

In the very act of the passage of the leucocytes through the vessel-wall, a certain chemiotactic or physiotactic influence is manifested. If we agree with Massart and Bordet [1] in considering this emigration as a mere effect of tactile sensibility, we cannot explain the fact that the leucocytes remain inside the vessels in cases when these are sufficiently dilated but when there may be in the neighbourhood substances which have a repellent action on leucocytes. Some time ago Binz found that no diapedesis of white corpuscles took place through the frog's mesentery after this had been moistened with a solution of quinine. As quinine acts poisonously upon protoplasm, it was concluded that it paralysed the leucocytes which were consequently unable to pass through the vascular wall. The same experiments were repeated by Disselhorst [2] who confirmed the fact that the diapedesis of the leucocytes ceased, but was astonished to find that their movements were not paralysed, for when removed from the vessels, the leucocytes showed their wonted amœboid activity. In order to explain these facts, Disselhorst maintained that the assistance of the vessel-wall was indispensable for the passage of the leucocytes, and that the diapedesis

Fig. 61.—Diapedesis of a leucocyte through the wall of a capillary, in which the blood is motionless.

[1] Journal published by the *Soc. roy. d. Sciences médicales et naturelles de Bruxelles*, 1890, vol. v.

[2] *Virchow's Archiv*, 1888, vol. cxiii., p. 108.

was prevented by the action of the quinine upon the wall. In his arguments, no account is taken of the chemiotactic property of leucocytes, which was not at that time an accepted fact. If this function be admitted, the effect of the quinine may be referred to a negative chemiotaxis of the leucocytes, which, although retaining their mobility, do not move towards the part moistened with this substance. It follows that the leucocytes are able, while still within the vessels, to detect the presence of the quinine.

The same explanation may be applied to the cases of infection by highly virulent microbes where the leucocytes, in spite of the dilatation of the vessels, do not cross the vascular wall. Thus in the most rapidly fatal infectious diseases, such as chicken cholera, septicæmia of guinea-pigs and pigeons, and many others, there is scarcely any emigration towards the invaded spot. In these cases no diapedesis takes place although the most favourable conditions exist, i.e. considerable inflammation and hyperæmia accompanied with serous and even hæmorrhagic exsudation. This may be explained by a negative chemiotaxis manifested by the intravascular leucocytes. This view is moreover borne out by the fact that the microbes of the above-mentioned diseases are not englobed by the leucocytes when brought into contact with them. The occurrence of chemiotactic action within the vessels necessarily follows from the leucocytosis produced by the absorption of various substances formed by the bacteria.

Massart and Bordet succeeded in stopping diapedesis by depressing the sensibility of the leucocytes with paraldehyde and chloroform, although these drugs did not paralyse their power of movement.

It is highly probable that various other sensibilities, besides those of touch and chemiotaxis, help in bringing about the act of emigration. In lesions where the necrosis of the cells is very slight and where consequently the attraction due to chemiotaxis can only be insignificant, we may probably regard the physical change in the medium (difference of tensions, &c.) as the chief factor in determining an attraction of the leucocytes.

The diapedesis of the leucocytes is usually preceded by the peripheral distribution of these cells in the dilated vessel. This phenomenon, to which the name '*itio in partes*' (Samuel) has been given, is generally considered to be the most mechanical event in inflammation. It was first sought to explain it by comparison of the movements of the spherical white corpuscles with the rapid motion of the flattened red blood discs ; but afterwards the explanation suggested by Chklarewsky[1] in his account of a research carried out in Helmholtz's laboratory, was adopted. This explanation is based on the fact, discovered by Mach and Bondi, that insoluble corpuscles when suspended in a fluid, increase the density of the mixture. Now as the corpuscles circulate only in the axial portion of the vessel, while the clear plasma flows along the sides, the density of the latter must be less than that of the central portion. As the leucocytes have a lower specific gravity than the red blood-corpuscles, they are driven from the denser axial current to the peripheral zone.

Although we must admit that the peripheral distribution of the leucocytes can only be due to a mechanical action, since according to Massart and Bordet the

[1] *Pflüger's Archiv für Physiologie*, vol. i.

white corpuscles, after being anæsthetised by chloroform, still proceed towards the sides of the vessels, yet we are unable to adopt the generally received explanation of this phenomenon. It has been known since Cohnheim's time and confirmed by Chklarewsky himself as well as by other observers that the peripheral distribution, as well as emigration, goes on just as well after the leucocytes have taken up vermilion granules. As these leucocytes now contain a mercurial salt, they must be not only heavier than they were before, but also heavier than the red blood-corpuscles. Nevertheless the latter remain in the axial current while the weighted leucocytes proceed towards the periphery.

The attraction of the leucocytes for the vascular wall has been referred by Hering to their adhesiveness. This theory has, however, found few supporters, for the reason that leucocytes are not sticky and do not become attached on account of their consistency but solely by means of their amœboid properties. Anyone may be convinced of the fact that naked protoplasm is not sticky by feeling the large plasmodium of the Myxomycetes, such as that of the *Spumaria alba*.

If it were possible to admit that the sensibility of the leucocytes in Massart and Bordet's experiments was not completely abolished by the action of chloroform, we might attribute their accumulation in the peripheral zone of the dilated vessels to a remnant of sensibility by which they could still appreciate the differences in the external medium, and so would move towards the calmer regions where they are free to extend their protoplasmic processes.

The vascular wall, by virtue of the power of contraction possessed by its endothelial cells, may no doubt

aid the passage of the leucocytes, although the latter are quite capable of traversing non-contractile membranes such as the epithelial tissues of vertebrates (Stöhr) or Ascidians. But the contractility of the endothelial cells must have more influence in regulating the passage of the red blood-corpuscles and the liquid parts of the blood, especially in those cases where, as in the infectious diseases mentioned above, the leucocytes in consequence of negative chemiotaxis remain in the blood, while the plasma and blood-discs exsude through the vascular wall.

Although the leucocytes may emigrate from the venules even when these are normal or only slightly dilated, (as Recklinghausen first observed in tadpoles under normal conditions,) it is nevertheless undeniable that the dilatation of the vessels accompanied by slowing of the blood-stream offers a very favourable condition for the occurrence of diapedesis. This dilatation, which is so constant in the inflammation of vertebrates, is a very complicated phenomenon in which several factors take part. Cohnheim,[1] who ascribed it exclusively to the action of the vascular wall itself, sought to prove his point by the following experiment. After pinning out the tongue of a frog on a disc of cork, he cut all the tissues connecting it with the body, with the exception of the artery and vein. In this way he considered that he had eliminated any possible nervous influences. He then applied some irritant to the tongue, and found that an inflammatory reaction was produced as usual. Cohnheim would not admit the possibility of local nervous mechanisms in the vascular

[1] "Gesammelte Abhandlungen." 1885, p. 423.

wall, although it is very probable that such mechanisms do play a part in these phenomena.

A considerable importance in the production of inflammatory hyperæmia is generally ascribed to the state of tension in the tissues, which is supposed to react on the capillaries. This idea, started by Fluss, was afterwards supported by Landerer,[1] who undertook a series of experiments to show that the tension in the tissues during inflammation is much lower than under normal conditions. The capillaries surrounded by these inflamed tissues are unable to withstand the pressure of the blood and therefore dilate. The immediate effect of this dilatation is an acceleration of the movement of the blood, which rushes in to fill the widened capillaries. But after a certain lapse of time, as the surrounding tissues lose their elasticity more and more, the blood-stream slows, thus producing the condition of the circulation typical of inflammation.

This theory also suffers from the disadvantage that it takes no account of the part played by nervous influence, which has been so much studied of late years. Samuel[2] has in the following experiment strikingly shown the importance of this influence. After cutting the sympathetic nerve in a rabbit on one side, he divided both auricular nerves on the other side of the same animal. Paralysis of the vaso-motors at first produced congestion of the ear on the side of the divided sympathetic and, as an indirect effect, a certain degree of anæmia in the opposite ear. This anæmia increased greatly after section of the sensory nerves, on account

[1] "Ueber die Gewebsspannung," 1884, and "Zur Lehre von der Entzündung." Leipzig, 1885.

[2] *Virchow's Archiv*, 1890, vol. cxxi., p. 396.

of the impossibility of reflex action by the uninjured sympathetic. If, however, inflammation was produced by treating both ears with hot water (at 54°), totally different results were obtained. The ear on the side of the divided sympathetic became very hyperæmic and highly inflamed. In the other ear, no hyperæmia occurred, and inflammation was replaced by a stasis ending in gangrene. This experiment proves the influence of the nervous system on inflammatory reaction and at the same time the beneficial effects of the latter. On the side where the inflammation is exaggerated in consequence of the paralysis of the vasomotor nerves, the ear is speedily restored to a normal condition, whereas the morbid phenomena are exceptionally severe on the anæmic side, where, owing to the division of the sensory nerves, the processes of inflammation are unable to take their usual course.

In the rabbits in which Samuel divided the sensory nerves (auricularis major and minor) on one side only, the results were much less serious. If the ears of these rabbits were dipped into water at 54°, in adult animals the inflammation followed the normal course, and it was only in young animals which had been treated in this manner that he observed a retardation of the inflammatory reaction and of the subsequent healing process.

Similar experiments have been made by Roger.[1] But instead of producing inflammation with hot water, he made use of the cultures of the streptococcus of erysipelas. He first divided the sensory nerves of one ear of a rabbit and then inoculated both ears with these bacteria. In the ear of which he had divided the

[1] *Comptes rendus de la Soc. de Biologie*, 1890, No. 34, p. 646.

auricular nerves, the erysipelas lasted a long time, and the healing processes, which were very slow, were accompanied by some mutilation of the organ, whereas in the normal ear of the opposite side the erysipelas ran its usual course.

The contrary result was obtained by Roger[1] on inoculating rabbits with erysipelas, after dividing the sympathetic instead of the sensory nerves on one side. The paralysis of the vaso-motors thus produced gave rise to a condition of hyperæmia, which exercised a favourable influence on the course of the erysipelas compared with the other ear where the sympathetic was intact. Inflammation began much earlier and the ear healed more rapidly on the side on which the sympathetic had been divided than on the other, although here also a cure finally resulted.

These experiments confirmed those of several other authorities, as Snellen, K. Danilewsky and others, who had observed an improvement in the course taken by the inflammation after division of the cervical sympathetic nerve. Since section of this nerve on one side also affects the ear of the opposite side by rendering it anæmic, Samuel modified his experiment in the following way. Instead of setting up inflammation in both ears of the same rabbit, he made use of two different rabbits, in one of which he divided the sympathetic on one side, while the other animal was left uninjured. He produced inflammation in the operated rabbit by the application of water at 54° to the ear on the side of the section, and in one ear of the normal rabbit by the same means. He then found that the inflammation

[1] *Comptes rendus de la Soc. de Biologie*, 1890, No. 16, p. 222.

ran a milder course in the control animal than in the operated rabbit.

All these experiments prove that the nervous system has a certain influence on inflammation, but at the same time shows that the influence only serves to accelerate or retard its course. While duly acknowledging that it plays this part, we must be careful not to exaggerate its importance, as by so doing we may fail to recognise the true relations of the different factors which co-operate to produce the inflammatory reaction.

It has been shown by Charrin and Gley [1] that reflex dilatation of the vessels can be prevented by injection of 20 c.c. of the soluble products of the bacillus pyocyaneus into the circulation of a rabbit. After this injection, these authors observed that "the vasodilatation thus produced develops more slowly, besides being less marked and of shorter duration," (p. 734) than under normal circumstances. In a later note [2] they proved that this inhibitory influence on the vascular dilatation is due exclusively to the volatile products contained in the cultures and is not shared by the non-volatile constituents, whether soluble or not in alcohol. These facts they refer to a diminution of the excitability of the vasodilator mechanism under the influence of these volatile products. According to them the secretions of the microbes diminish dilatation, hinder diapedesis and in this way favour the course of the infection. They seek to apply these results to the explanation of immunity ; thus vaccination would act by strengthening the part of the nervous system which presides over the dilatation of the blood-vessels and over diapedesis.

[1] *Archives de Physiologie*, No. 4, 1890, p. 724.

[2] *Ibid.*, No. 1, 1891, p. 146.

Charrin and Gamaleïa[1] have likewise prevented the dilatation of the blood-vessels by the injection of vaccines or of the products of the micro-organism of vibrionian septicæmia, as well as by simple injections of 5-10 per cent. solutions of salt.

We cannot suppose that in the natural course of an infective disorder there is a sudden entry into the blood of 20 c.c. of bacterial products. In order then to come to a decision on the subject, we must experiment on animals which have been inoculated with the microbes in question. If we introduce some bacillus pyocaneus from a culture on agar-agar under the skin of two rabbits, one of which has not been treated, while the other has been vaccinated against the malady produced by this bacillus, the inflammation produced is much more marked in the first rabbit than in the vaccinated animal. In the former the bacterial products prevent neither the vascular dilatation nor the increased local temperature, nor the serous exsudation at the point inoculated; and yet the diapedesis is less than in the vaccinated rabbit, in which on the other hand the vasodilatation and increase of temperature are much less pronounced. The difference is still more striking if we compare the results of injecting the vibrio of septicæmia (*Vibrio Metchnikowii*) under the skin of the ear in two guinea-pigs, one of which is susceptible, while the other has been rendered refractory by means of vaccinations. Here we find that the reddening, heat and tumefaction are much more marked in the susceptible than in the immune animal, whereas diapedesis which is well marked in the vaccinated animal scarcely occurs at all in the other.

[1] *Centralblatt f. allgemeine Pathologie*, Nos. 18, 19, 1890, vol. i., p. 588.

These facts show in the first place that, contrary to the conclusions of Charrin and Gley, the microbes in question do not hinder the vascular dilatation in susceptible animals; and, in the second place, that diapedesis may be almost or entirely absent in spite of considerable dilatation of the blood-vessels. We must conclude therefore that the most important factor in the production of diapedesis is the sensibility of the leucocytes themselves. If this sensibility be positive, the leucocytes emigrate, in spite of the insignificant dilatation of the vessels; if it be negative, diapedesis is not produced, however dilated the blood-vessels may be. This fact may be easily shown by using for inoculation a microbe exercising considerable positive chemiotaxis on the leucocytes. If two guinea-pigs be inoculated under the skin of the ear, one with a small amount of tubercle bacilli and the other with the vibrio Metchnikowii, in the first animal the dilatation will be slight and the diapedesis very considerable, while in the latter the dilatation will be marked but will be accompanied by little or no diapedesis.

The following facts may also serve as indirect arguments against Charrin's and Gley's interpretation of their results. In the most acute infections, in which diapedesis is nearly or entirely absent, the presence of leucocytes does not in any way hinder the existence and multiplication of the bacteria, since in consequence of a negative chemiotaxis the leucocytes do not englobe these microbes. Under these circumstances it would be quite superfluous to hinder diapedesis. If then, instead of introducing some of these malignant bacteria (such as the bacillus of chicken cholera in birds and rabbits, or the vibrio of avian septicæmia in guinea-pigs and

pigeons) into the subcutaneous tissue, we introduce them directly into the blood, the result is exactly the same. The animals die in a very short time without the occurrence of any phagocytosis; and it makes no difference to the issue whether, as in this case, the bacteria are in close proximity to the leucocytes in the blood and spleen, or whether, as after subcutaneous inoculation, they are at some distance from these cells, which remain in the interior of the blood-vessels.

We must therefore look upon the sensibility of the leucocytes as the most important factor in inflammatory diseases, not forgetting however the part played in the inflammatory reaction in vertebrates by the sensibility of the endothelial cells, as well as by that of the nervous and other elements.[1]

[1] See my lecture on "Immunity" in the *British Medical Journal* of January 31st, 1891. After I had written this chapter, Massart and Bordet put forward the same ideas in a study of the chemiotaxis of leucocytes in infectious disorders (*Annales de l'Institut Pasteur*, 1891, p. 417). They concluded from these experiments that the absence of diapedesis in certain infectious disorders is due not to a paralysis of the vasomotor centres, but rather to a negative chemiotaxis of the leucocytes. In consequence of this paper, a controversy has arisen between Charrin and Gley on the one side and Massart and Bordet on the other (*Comptes rendus de la Soc. de Biologie*, 1891, pp. 703–710. See also Bouchard, *Comptes rendus de l'Acad. des Sc.*, 1891, pp. 524–529). Without entering into the details of this discussion, we may state generally that it is not a vasomotor paralysis but a negative chemiotaxis which is the real cause of the absence of leucocytes at the seat of the lesion in certain severe bacterial infections. Hertwig ("Physiologische Grundlage der Tuberculinwirkung." Jena, 1891) and Buchner (*Münchener medicinische Wochenschrift*, 1891) have also pronounced in favour of this view.

LECTURE X.

Chronic inflammations—Tuberculosis as a type of a chronic inflammation—Phagocytic nature of tuberculous cells—Destruction of tubercle bacilli by phagocytes—Power of resistance of *Meriones* to tubercle—Leprosy.

HAVING passed in review the principal elements involved in inflammation in the vertebrata, it remains to inquire whether the part played by each is invariably the same in all cases of inflammatory reaction. In acute inflammation we find as a general rule vascular dilatation accompanied by an active condition of the endothelium of the vessel-walls and an exsudation with diapedesis, that is to say, three events which concur in producing a considerable afflux of leucocytes towards the injured spot. Is the order of phenomena the same in the chronic inflammations? We often meet with the idea that whereas in acute inflammation vascular changes accompanied by diapedesis play the most important part, in chronic inflammation the greatest significance must be attributed to local phenomena that take place in the tissues without the co-operation of the cells of the blood or blood-vessels.

Chronic, like acute inflammations, are due to various causes, which may be chemical, physical, or, as is more usually the case, biological in nature. They may be

brought about by the slow action of any injurious substance, as lead, phosphorus or alcohol, or by the prolonged action of heat or other harmful physical means; but they are more frequently the immediate effect of microbes and their poisonous products.

We may take as an instance the chronic inflammation which results in the production of tubercles in bacillary tuberculosis or in some other granuloma. We choose this type, not only on account of its great importance in pathology, but also because the fixed elements of the tissues have been regarded as the chief factors which contribute to its formation. According to Baumgarten's theory,[1] which is accepted by most pathologists, the phagocytic cells in general and the leucocytes in particular take little or no part in the formation of the tubercle itself. This he considers to be produced by a proliferation of the local tissue cells, excited by the presence of the tubercle bacillus in their neighbourhood. Thus, according to this view, pulmonary tubercle is developed at the expense of the epithelial cells of the alveoli; hepatic tubercle at the expense of the liver-cells and the epithelial cells of the bile-ducts; renal tubercle by a proliferation of the epithelial cells of the urinary tubules, &c. The connective tissue also contributes to the formation of tubercle by means of its fixed cells and endothelial cells. The leucocytes take no part in the formation of the tubercle until a later period and hence must be regarded as of merely secondary importance. According to this theory, tuberculosis would not be a true inflammation, otherwise we must admit that a chronic inflammation may

[1] "Tuberkel und Tuberkulose." Berlin, 1885. Reprinted from the *Zeitschrift f. klin. Medicin.*

be developed almost entirely independently of the phagocytes or of the leucocytes.

The formation of tubercle may be accelerated by injecting bacilli of avian tuberculosis into the veins of rabbits, which, as is well known, are very susceptible to this disorder. At the end of a few days, microscopic tubercles are developed which may serve as a type of this class of neoplasm. If we examine the liver, we shall see that the epithelioid and giant cells of the tubercles are formed solely at the expense of the phagocytic elements, that is to say, of the large mononuclear leucocytes and of Kupffer's star-cells, derived from the vascular endothelium. No hepatic or epithelial cells ever contribute to the production of tubercle. It is true that their nuclei may occasionally be seen about to undergo karyokinetic division; but this proliferation has no direct connection with the formation of tubercle, and merely serves for the regeneration of the hepatic cells themselves.

Hepatic tubercle is the result of an accumulation, not a multiplication of the mesodermic phagocytes, which collect in masses and make up the whole of the original tubercle. These phagocytes contain bacilli which have been englobed by the amœboid cells. Several of the epithelioid cells fuse together to form giant cells, while the tubercular elements are reinforced by a large number of lymphocytes and mononuclear leucocytes. Although the former are not yet leucocytes, they soon become converted into epithelioid cells, which represent one variety of leucocytes.

Hepatic tubercle is therefore not derived from various sources, as Baumgarten maintains, but is produced by the amœboid and phagocytic cells of the mesoderm.

The mode in which pulmonary tubercle is developed confirms this view. This variety of tubercle is formed by the endothelial cells of the blood-vessels together with the leucocytes, and is the result not of the proliferation but of the accumulation of these cells, which is effected by means of their amœboid movements. The cells of these tubercles likewise show their phagocytic properties by englobing the tubercle bacilli. In cases where 'dust-cells' ('Staubzellen') contribute to the formation of tubercles, we have again to do with phagocytic elements derived from mononuclear leucocytes.[1]

Tubercles of the spleen and of the lymphatic glands are likewise formed by an agglomeration of the larger phagocytes of these organs—phagocytes possessing a single large nucleus. In guinea-pigs and marmots (*Spermophilus*) a study of the neoplasms produced by the bacillus of avian or human tuberculosis further confirms the statement that *tubercle is composed of a collection of phagocytes mesodermic in origin, which move towards the spot where the bacilli are situated and englobe them.* The phagocytes retain their condition of epithelioid cells, or are transformed into giant cells. The latter can also be formed in another way, although in any case the final result is a large mass of protoplasm enclosing a number of nuclei. In some animals, as the marmots, the nuclei proliferate by a process of budding; more frequently however the multiple nuclei are derived from a number of cells which have fused to form a plasmodium. It is possible that the nuclei may

[1] See Tchistowitch, *Annales de l'Institut Pasteur*, 1889, p. 337. Afanasieff, in an investigation carried out in my laboratory on the development of pulmonary tubercle in the rabbit after inoculation of tubercle bacilli from man, proved that here also the tubercle is a purely phagocytic product.

also multiply by karyokinesis, but this has never been demonstrated with certainty.

It is a well established fact that leucocytes take part in the formation of tubercle, but these leucocytes belong to the mononuclear variety. The polynuclear cells englobe the tubercle bacilli readily but perish after a short time, and then with the microbes they contain, are eaten up by various mononuclear phagocytes which may be classed together under the term of *macrophages*. These latter cells have a much greater power of resistance, and in some cases are even capable of destroying the tubercle bacilli. Thus after inoculating marmots with avian or human tubercle I have observed a very characteristic degeneration of the bacilli in the interior of the epithelioid and giant cells of these animals, which are but little susceptible to tuberculosis.[1] The bacilli, evidently under the influence of these cells, swell up and gradually lose their power of retaining colouring reagents. Sometimes the peripheral part but more often the central part of the bacillus is the first to lose its coloration. Later on the bacillus becomes converted into a yellowish sausage-shaped body, enclosing a very delicate canal, and the altered microbes collect to form a conspicuous brownish mass, having the characteristic aspect of a fragment of amber. None of these changes

[1] See my article in *Virchow's Archiv*, 1888, vol. cxiii., p. 63. The facts brought forward in this paper concerning tuberculosis in marmots refer to the bacillus of avian tuberculosis. Later experiments have shown me that this animal is more susceptible to the bacilli of human tuberculosis, although, even in this case, a certain number of bacilli are destroyed in the cells and converted into yellow particles. At the Congress in London, Bardach brought forward facts showing the high degree of susceptibility possessed by the marmots for the virus of human tuberculosis, which he made use of in his experiments.

are ever observed in artificial cultivations, even though a number of dead bacilli are present, nor indeed anywhere outside the tubercular cells. They must be therefore regarded as resulting from the phagocytic action of these cells, and recall the degenerative phenomena which have been described in an earlier chapter as taking place in cysts of the Gregarinæ and the larvæ of the Nematoda, when surrounded by the phagocytes of Lumbricus. In all these cases we have to do with abnormal secretions poured out by the parasites in order to resist the influence of the phagocytes which enclose or surround them.

Bacilli have also been ascertained to undergo changes similar to those just described, within the giant cells of rabbits, and very occasionally within those of guinea-pigs. On the other hand I have never been able to detect bacilli which have been destroyed by these means either in the tuberculosis of Bovidæ or of man. And yet the resistance offered by the organism in such cases is often of a very marked character. Calcareous degeneration of tubercle has long been recognised as a means by which tuberculosis in human beings may be cured. In order to give a better idea of this reactive phenomenon, I will describe the manner in which the Algerian rat (*Meriones*) succeeds in resisting the action of the tubercle bacillus. This rodent, although not entirely immune against tuberculosis, receives it in a milder form than many of the allied species. If inoculated under the skin or even in the eye with a culture of the bacilli of human tuberculosis, this animal withstands the effects of the disease for many months.

If an Algerian rat that has been inoculated six or eight months previously, be killed, a large number of

tubercles are found in the abdominal organs, the lungs and the lymphatic glands. These tubercles, however, in the majority of cases, do not present any necrosis or caseation. The tubercular tissue composed of living cells encloses bacilli, the majority of which have undergone a very remarkable degeneration, which deserves our further consideration. In this animal the main struggle goes on in the spleen, which is studded with small tubercles consisting of non-necrosed epithelioid and giant cells. The former cells enclose a small number of ordinary tubercle bacilli, while the giant cells contain characteristic calcareous bodies. (Fig. 62.) When examined under the microscope they are seen to be highly refracting and in the majority of cases to have the shape of a figure of eight, although sometimes they are simply rounded or irregular in form. Under the influence of acids, the lime salt (phosphate of lime) may be dissolved out, leaving a skeleton consisting of a larger or smaller number of fine concentric layers. (Fig. 63.)

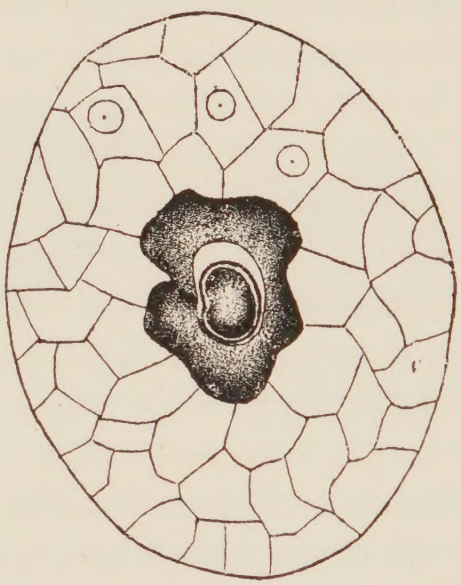

Fig. 62.—Tubercle from Meriones enclosing a calcareous body.

These calcareous bodies have a strong resemblance to the formations described by Schüppel[1] as occurring

[1] "Untersuchungen über Lymphdrüsen-Tuberkulose." Tübingen, 1871, p. 104 and Pl. I., Fig. 3, 4.

in scrofulous glands, and observed by several authors [1] in many cases of tubercle of the lymphatic glands in man. (Figs. 64, 65.) But whereas the origin of the striated calcareous bodies in man is still quite obscure, it can be demonstrated in Meriones with the utmost facility. The examination of cover-glass specimens or sections doubly stained by the methods of Gram or Ziehl, shows at once that these bodies are the result of a degeneration of the tubercle bacilli in the interior of the giant cells. In the early stages, the bacilli stain in the usual manner, and do not present any noticeable

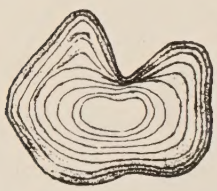

Fig. 63.—The same calcareous body treated with a dilute acid.

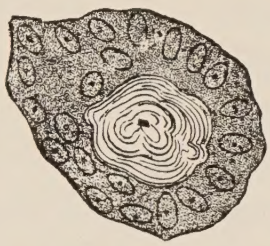

Fig. 64.—Tubercle containing a calcareous body. From a human scrofulous gland. (After Schüppel.)

Fig. 65.—Calcareous body fram a mesenteric gland of man. (After Ziegler.)

features. But by the side of these, we see other giant cells (Tab. III., Fig. 4), in which the bacilli (*a*) are covered with a fairly thick layer of an amorphous, colourless substance (*b*). This secretion becomes more and more abundant so that the bacilli are finally surrounded with a number of concentric layers. In many cases these microbes may be stained with gentian violet or fuchsin in the usual manner, but more frequently they lose this power and take up the complementary stain. (Tab. III., Fig. 5.) Sometimes in the centre of a calcareous body, we meet with a bacillus divided into two, half of which still retains the primary

[1] Ziegler, "Lehrbuch der patholog. Anat.," 6th Edition, 1890, vol. ii., p. 98, Fig. 50.

coloration while the other has already lost it. (Tab. III., Fig. 6.) Thus passing through a series of intermediate changes, the bacillus arrives at a condition when it will no longer take the stain, although its contour is still well-marked. (Tab. III., Fig. 7.) Later on, however, they are not to be distinguished by their coloration from the surrounding substance, (Tab. III., Fig. 8) and finally disappear completely. (Tab. III., Fig. 9.) In the last stage, which is most frequently met with, we see nothing but the stratified calcareous bodies.

The concentric membranes, which are left after the removal of the phosphate of lime by means of dilute acids, consist of a substance identical with that which constitutes the envelope of the tubercle bacillus. Like the latter, they are dissolved by concentrated acids, they are not affected by alkalies, and do not give a red colour with Millon's reagent. These facts must lead us to the conclusion that the concentric layers are secretions of the tubercle bacilli and are exactly analogous to the stratified cuticle which, as we have seen, becomes formed round the Gregarinæ and Nematoda when attacked by the phagocytes of Lumbricus (p. 69). Thus in Meriones the bacillus defends itself against the giant cell in which it is lying by the secretion of a series of envelopes. On the other hand it is very probable that the phosphate of lime is laid down by the giant cell itself in its reaction against the bacillus.

The struggle between these two living bodies—the tubercle bacillus and the giant cell of Meriones—is thus carried on by means of secretions. The bacillus defends itself by the secretion of cuticular membranes, and probably also by the production of toxines, while

the giant cell secretes a calcareous deposit by means of which it walls in the bacillus, and usually succeeds in killing it. The giant cell probably also produces digestive fluids which aid it in attacking and digesting the bacillus.

For the deposition of phosphate of lime to take place in the interior of the giant cell an alkaline medium is required. The alkaline reaction of the contents of the giant cell and of the calcareous body formed from the bacillus may be shown by various reagents such as the sulpho-acid of alizarin, which is a very delicate test for the presence of alkalies and gives these structures a pronounced violet colour. Their intense coloration with hæmatoxylin points to the same conclusion (Tab. III., Fig. 8).

The exact conditions of this struggle between the microbe and the phagocyte are highly interesting and important and will form the subject of a separate experimental investigation. Here I will only lay stress on the conclusion that the giant cells, so characteristic of tubercle, really represent a special form of phagocytes, which are particularly energetic in the conflict with the microbes. This is moreover confirmed by the discovery of Soudakewitch,[1] that the giant cells of lupus are able to digest the elastic fibres of the skin. To attack substances so resistant as tubercle bacilli and elastic fibres requires very active power of digestion. In this respect the giant cells of tubercle may be compared to the giant cells known as osteoclasts, which effect the absorption of bone.

Weigert,[2] whose view on this point is accepted by

[1] *Virchow's Archiv*, 1889, vol. cxv., p. 264.

[2] *Deutsche med. Wochenschr.*, 1885, and *Fortschritte der Medicin*, 1888, p. 809.

Koch[1] and other pathologists, considers that the giant cell of tubercle represents a condition of partial necrosis, by which the division of the protoplasm is prevented. Against this theory, besides the above-mentioned fact of the remarkable power of resistance possessed by these cells, we may cite their property of dividing into smaller cells. It is not surprising that this division should be unaccompanied by karyokinetic phenomena, since here the nuclei are multiple to start with, and all that is still necessary is the division of the protoplasmic body of the cell.

If we accept the opinion put forward by various authors and lately revived by Chun[2] that fragmentation of the nucleus, by enlarging its surface, may serve to heighten the activity of the intracellular processes of nutrition, it is easy to understand the teleological reason for the increase in the number of nuclei in the cells which have to digest bodies so resistant as those in question. We must not forget that in many invertebrate animals plasmodia are often formed during the process of intracellular digestion, these fused agglomerations of cells being very commonly met with in the phagocytic reaction of Sponges, Medusæ, Echinoderms, Molluscs, Daphniæ, &c.

The cells of tubercle, which serve the organism in its reaction against the microbes, are often destroyed by the action of the bacilli, and then form the necrosed caseous masses so characteristic of this disorder. This degeneration is probably due in some degree to the fact that the tubercles do not contain any blood vessels, so that the activity and vitality of the phagocytes suffer

[1] *Deutsch. med. Woch.*, 1891, No. 3, p. 102.

[2] *Physik.-ökon. Gesellschaft zu Königsberg.* April 3rd, 1890.

from lack of nourishment. Koch has found that if the inflammatory process in the tubercles be increased by injection of tuberculin, a striking improvement may be produced in the condition of guinea-pigs, and many experimenters have observed a temporary amelioration in man, after the same procedure. Probably in this case the cells of the tubercles are better nourished in consequence of the inflammatory hyperæmia that is set up, so that they become more active and better fitted to resist the action of the bacilli.

The type of chronic inflammation that we have chosen has shown us that the essence of the process consists in a reaction of mesodermic phagocytes against the offending agent. Although the macrophages are more conspicuous than the leucocytic elements, yet we must remember that among the macrophages of tubercles a large number of mononuclear leucocytes also occur; and Ehrlich[1] has shown that the latter elements are markedly increased in the blood of phthisical patients.

Another chronic disorder, leprosy, which is analogous in many respects to tuberculosis, must also be regarded as a struggle between the mesodermic phagocytes and the specific bacillus—a struggle which lasts for many years. Although the origin of the macrophages is not yet known with certainty, it is probable that they are derived from the endothelial and connective tissue cells, as well as from the mononuclear leucocytes. These cells unite to form granulomata, and destroy the bacilli that they englobe, thus acting as phagocytes.

[1] *Charité Annalen*, 1887, vol. xii., and "Farbenanalytische Untersuchungen," 1891, vol. i., p. 124.

The older researches of Neisser[1] and Kebner,[2] as well as the more recent ones of Soudakewitch[3] and Sawtchenko[4] leave no doubt as to the general characters of the cellular pathology of leprosy. Having had several opportunities of studying leprosy of the skin and of the liver (among others in the preparations of Muskatbluth made in my former laboratory at Odessa), I am able to confirm the fact that in these cases the leprous cells possess all the characteristics of mesodermic phagocytes. In the liver the cells which englobe the leprosy bacilli are chiefly of the endothelial type, with an extraordinary number of vacuoles in their protoplasm. From the point of view of the phagocytic theory, this vacuolar 'degeneration' should rather be regarded as due to an abundant secretion of digestive fluids, analogous to that observed in the Protozoa while intracellular digestion is going on. In the interior of leprous cells, especially those of the skin, we often find enormous numbers of dead bacilli, showing the therapeutic action of these cells. The fact that Boinet and Borel[5] have not been able to confirm this function of the cells shows either that they had to do with special cases, or what is more probable, that their observations were incomplete.

Among the tubercular diseases one that has been recently studied by Ebstein and Nicolaier[6] has a special interest for us, *viz.*:—the tubercular affection

[1] *Virchow's Archiv*, 1881, vol. lxxxiv., p. 520.
[2] *Ibid.*, 1882, vol. lxxxviii., p. 299.
[3] *Ziegler's Beiträge zur pathol. Anat.*, vol. ii., Pt. i.
[4] *Ibid.*, vol. ix. p. 241.
[5] *Comptes rendus de la Soc. de Biol.*, 1890, p. 38.
[6] *Virchow's Archiv*, 1889, vol. cxviii., p. 432, pl. xiii., xiv.

produced by Nematoda in the kidneys of dogs and the lungs of cats. In these cases the larvæ become surrounded by veritable tubercles, composed in the dog of epithelioid cells alone, and in the cat of these together with giant cells. In the dog each tubercle contains a living larva enclosed by masses of tubercular cells. Here then we have an undoubted instance of an aggregation of leucocytes around a living animal, recalling forcibly the collection of phagocytes in Lumbricus round the living larvæ of Rhabditis, as described in the fifth lecture. It demonstrates once more the fact that an accumulation of leucocytes may be provoked by the presence of living organisms, and does not require the presence of dead substances, or substances derived from the dead bodies of the parasites. Unfortunately, however, these cases of zooparasitic tuberculosis have not yet been sufficiently studied to give us any accurate knowledge as to the origin or development of the cellular elements composing the tubercles.

As Brault[1] has pointed out, there is a striking analogy between the chronic inflammation brought about by the tubercle bacillus and the processes that give rise to the disease known by the name of *hypertrophic cirrhosis*. In both cases we have a reaction of the connective tissues, or rather of the mesodermic cells in general, a reaction which extends over a prolonged period. Even if we regard it as an established fact that the cirrhoses are produced directly by chemical poisons such as lead, alcohol and others, the analogy of the pathological processes in the two instances is by no means destroyed. In the chronic infectious inflamma-

[1] *Archives générales de médecine*, 1888, p. 47.

tions the phagocytes collect around the parasites, whereas in the cirrhoses they attack the tissue-cells that have been enfeebled under the action of the poisons. The final results then in the two cases may be quite different, since in one the phagocytes destroy the microbes, while in the other they annihilate the cells belonging to the organism itself. In this respect the chronic inflammations are closely allied to the phenomena of atrophy, which however are scarcely within the range of these lectures.

LECTURE XI.

Serous inflammations—Two classes of these inflammations—Bactericidal power of the humours and the serous exsudations—Antitoxic property of serum and the serous inflammations.

IN the chronic, as in the acute inflammations, whether purulent, fibrinous or catarrhal, we find that a pronounced phagocytic action forms the key note of the whole process. In the serous inflammations, however, the number of leucocytes present is too small to permit of our ascribing any great significance to their presence. Up to the present our knowledge of these serous inflammations is very incomplete. So far as we can judge from experiments on animals, they may assume various forms.

In the first place there are certain inflammations which acquire the character of 'serous' in consequence of a negative chemiotactic influence on the leucocytes, which do not emigrate or move towards the seat of lesion, and therefore do not take any part in the formation of the exsudation. The walls of the vessels, however, react as usual, thus permitting the passage through their pores of the fluid forming the serous exsudation, which is almost entirely devoid of leucocytes. The exsudation often contains numerous pathogenic microbes which multiply rapidly in it without let or

hindrance. Deprived in this way of any phagocytic protection, the animal organism speedily becomes a prey to the microbes. In this class of serous inflammations we may include the most acute and fatal diseases, such as the vibrionic septicæmia of birds and guinea-pigs, anthrax in the smaller rodents as mice and guinea-pigs, and some other infectious disorders. In the form of septicæmia just mentioned, the vibrio swarms freely in the serous exsudation with its almost total absence of leucocytes. In the serous exsudation of animals infected with anthrax, the bacilli are only present in small numbers, although the fluid collects at or in the immediate neighbourhood of the infected spots.

In a second group of serous inflammations of microbic origin, the exsudation is formed in regions, which may be at some distance from the deposit of microbes, and does not contain any bacteria at all. Roux and Yersin [1] have shown that the exsudation produced in the serous pleurisy which often accompanies diphtheria in guinea-pigs does not contain any microbes, which remain localised at the seat of inoculation. In ten cases of serous inflammations accompanying phlegmonous erysipelas or other suppurative maladies, the liquid contained in the inflammatory œdema was found by Zimmermann [2] to be absolutely free from microbes. The question at once suggests itself whether this transsudation of fluid really represents a phenomenon of reaction on the part of the organism, and if so, what use it is to the infected organism.

In examining this point we naturally think first of a

[1] *Annales de l'Institut Pasteur*, 1888, p. 635.

[2] *Münchener medicinische Wochenschrift*, 1889, No. 9, p. 141.

possible microbicide action of the transsuded liquid which would rid the organism of its aggressors. We find, however, that all kinds of bacteria can live and flourish in the fluid of the inflammatory œdema. Although the serous exsudation of anthrax does not usually contain many microbes, it may nevertheless serve as a nutrient medium for them. Even in animals refractory to anthrax, the spores of this bacillus, if introduced into the serous fluid of the œdema produced by a primary inoculation of anthrax,[1] will germinate and give rise to a new generation of microbes. The small number of microbes found in the exsudation cannot therefore be taken as a proof of any bactericidal action of this fluid.

In human beings tuberculosis is also frequently accompanied by serous pleurisy in which no bacilli will be found. But their absence is not due to their having been killed by the liquid. If they had been present, they would, as is invariably the case, have attracted the leucocytes. As the microbe of diphtheria remains localised at the seat of inoculation, we cannot doubt that in this disease also there are no bacilli in the serous exsudation from the very beginning of the process. The above-mentioned ten cases of Zimmermann were diseases brought about by the streptococcus pyogenes and the staphylococcus, i.e. by two microbes which, as Stern[2] has proved, the serous exsudation of human beings is absolutely unable to destroy. And yet Zimmermann was unable to find any bacilli in the serous exsudation which he collected from the above cases.

[1] For a description of experiments of this nature on rats, see *Annales de l'Institut Pasteur*, 1890, p. 201.

[2] *Zeitschrift f. klin. Medicin*, 1890, vol. xviii., p. 62.

After this analysis of the facts so far as they are known, we cannot admit that serous inflammation is a means used by the organism for killing the pathogenic organisms. The results obtained with regard to the bactericidal properties of serous fluids generally are in confirmation of this conclusion. In spite of all the endeavours to prove that an active part is played by these fluids in the destruction of microbes and the production of immunity, we must recognise the fact that they are of no importance in this capacity. Further study of the bactericidal powers possessed by the serum has shown that these have no connection either with the phenomena which go on in the organism or with the production of immunity.

Behring, who was one of the chief originators of the bactericidal theory of the humours, carried out a large number of researches on the subject, and concluded by doubting whether the blood deprived of its cellular elements could really produce immunity.[1] The results of numerous experiments which he made with Nissen [2] led him to consider that the bactericidal property of the serum is only met with in a few isolated cases, where natural or acquired immunity exists at the same time. Among these cases, the most marked are the action of the serum of rats upon the anthrax bacillus and that of the serum of vaccinated guinea-pigs upon the *Vibrio Metchnikowii*.

Although the facts discovered by Behring and Nissen are perfectly correct, and we must regard it as established that the serum of rats has really a bactericidal action on anthrax bacilli, and the serum of vaccinated

[1] *Deutsche medicin. Wochenschrift*, 1891, No. 19, p. 655.

[2] *Zeitschrift für Hygiene*, 1890, vol viii. p. 424.

guinea-pigs on the *Vibrio Metchnikowii*, yet even in these cases these bactericidal powers which are so evident *in vitro* do not come into play in the body of the living animal. As Hankin,[1] Roux and I[2] have shown, although rats are not refractory to anthrax, yet their serum outside the body has a bactericidal action on the bacilli of this disease. Again the *Vibrio Metchnikowii* is readily destroyed *in vitro* under the influence of the serum of guinea-pigs which have been rendered refractory by vaccination, although if inoculated under the skin or in the eye of the same animals, these microbes live for some time and finally adapt themselves to their environment, so that they can now live in the serum prepared from these animals.[3]

The impossibility of drawing any conclusion as to the events that occur in the living organism, from the results obtained from experiments with the serum outside the body, was shown in the earlier researches of Lubarsch[4] and myself.[5] Recent experiments of Buchner, Ibener, and Rœder,[6] have also proved that the bactericidal properties of the serum, which are very evident when the serum is allowed to act upon the microbes in test tubes in the usual manner, become much less marked if the same microbes be introduced into the living body enclosed in capsules of filter paper, so that they may be acted upon by the fluids of the body without the possible interference of cells.

[1] *Centralblatt für Bacteriologie*, 1891, p. 378.
[2] *Annales de l'Institut Pasteur*, 1891, p. 479.
[3] *Ibid.*, p. 465.
[4] *Centralblatt für Bacteriologie*, 1889.
[5] *Virchow's Archiv*, 1888, vol. cxiv. p. 472.
[6] *Münchener medicin. Wochenschr.*, 1891, Nos. 32 and 33.

A review of these facts leads us to conclude that the exsudation of a serous fluid in inflammation cannot be regarded as a means which the organism may make use of to destroy the pathogenic microbes, this service being performed essentially by the phagocytes. Since, however, the poisonous chemical products of the bacteria are the most important agencies in producing the general intoxication that we know as the disease, it is possible that the serous exudation may serve to attenuate or modify the action of these products.

The remarkable discovery of Behring and Kitasato [1] that the serum of immunised animals possesses antitoxic properties, seems to tell in favour of this hypothesis. These observers who have been confirmed by Vaillard, Tizzoni, and Cattani, have shown that the serum of rabbits which have been vaccinated against tetanus, can destroy considerable quantities of the toxine of this disease. Behring [2] has obtained analogous, though not so perfect, results for diphtheria; and the Klemperers [3] have also proved that the blood and serum of rabbits which have been inoculated against pneumonia, as well as these fluids in men who have survived the crisis of a pneumonic attack, are endowed with antitoxic properties.

Is it possible that the serous exsudation, although incapable of killing the microbes, may serve to destroy the toxines? This supposition would seem to receive some support from the discovery by Behring of the diphtheritic poison in the pleuritic effusion of rabbits affected with this disorder. But in man, on the other

[1] *Deutsche medinische Wochenschrift*, 1890, p. 1113.

[2] *Ibid.*, p. 1145.

[3] *Berliner klinische Wochenschrift*, 1891, Nos. 34 and 35.

hand, although diphtheria often ends favourably, the production of serous exsudations is never observed.

If we may regard croupous pneumonia as a disease which terminates by producing an antitoxine (although this cannot be taken as proved, in spite of the statements of the Klemperers), it would furnish us with another instance of the destruction of a toxine occurring independently of any serous inflammation.

Tetanus is the type of a toxic disease. Yet although vaccination against it gives rise to a rich production of antitoxine, we never find any serous exsudation occurring in the disease itself. Vaillard, who has a large experience in the subject of tetanus, informs me that in no case are serous inflammations ever present either in animals affected with tetanus, or in those which are undergoing the process of immunisation by the injection of the serum of vaccinated animals.

On the other hand tuberculosis, which is so often accompanied by serous exsudations, must be looked upon as one of the diseases in which toxines play the smallest part. This is shown by the fact, among others, that the guinea-pig, which is so susceptible to tuberculosis, is remarkably insensible to the action of the tuberculin. As another example I may cite the Vibrio Metchnikowii. If this microbe be introduced into guinea-pigs, whether susceptible to or vaccinated against its action, an abundant serous exsudation is formed, and yet no antitoxine is produced in the animals that recover from the disease, as is shown by the fact that these animals, even when vaccinated against infection by this microbe, are still susceptible to the action of the toxine formed by the Vibrio.

Thus the hypothesis that a serous inflammation is a

salutary reaction of the organism, is not confirmed by the facts so far as we know them. We must keep in mind, however, that our knowledge on the subject of the production of antitoxines is in its infancy; and we must wait for much wider and more varied experience before we can come to a conclusion on the subject.

I may mention one more hypothesis. If we cannot look upon the exsudation of serous fluid as connected with the formation of antitoxines, it is at least possible that it may serve to dilute the bacterial toxines and so render them less active.

A study of comparative pathology shows that in the evolution of the inflammatory process the serous inflammations are much more recent than those which are merely attended with a leucocytic reaction. In none of the invertebrata, in which we have studied the accumulation of phagocytes around foreign bodies, is there any trace of a serous exsudation accompanying this process. This is true not only for the organisms which possess no blood (such as the Sponges, Cœlenterata and Echinoderm larvæ) but also for those endowed with a circulatory system. Even in the amphibians, in which the phagocytic reaction is so pronounced, the inflammation is unaccompanied by any marked transsudation of fluid. Only in a few exceptional cases have I observed a slight accumulation of fluid around inflammatory foci in the tails of tadpoles and of urodelan larvæ.

From whatever point we consider serous inflammation it appears as a phenomenon of minor importance compared with the typical inflammatory process, i.e. an accumulation of phagocytes in the inflamed area.

LECTURE XII.

Review of other theories of inflammation in light of the acquired facts—Nutritional theory of Virchow—Vascular theory of Cohnheim—Experiments of the latter on the tongue of the frog. Introduction of irritative agents into the blood. Argument against Cohnheim's theory furnished by the reaction in vertebrata—Struggle of the organism with external agencies—Use of intracellular digestion—Phagocytes—Hæmitis (recurrent fever, disease of Daphnia)—Tuberculosis. Essential nature of inflammation—Sensibility of the phagocytes—Its progressive development—Sensibility of the endothelial cells—Definition of inflammation. Inflammation is not regeneration—Inflammation is not identical with resorption—Objections raised to the biological theory of inflammation—Vitalism—Teleology—Absence of phagocytes in certain infective lesions—Imperfections in the inflammatory reaction—Surgical interference—Comparative pathology.

HAVING now reviewed the principal phenomena of the inflammatory reaction in the animal kingdom, we may ask how far the facts thus brought out are in harmony with the various theories mentioned in the first lecture.

It is unnecessary to insist more than cursorily on the impossibility of explaining these facts by the nutritional theory of Virchow.[1] This doctrine assumes that a greatly increased flow of nutritive substances takes place towards the inflamed part as well as abnormal

[1] "Cellularpathologie," 4th Edition, 1871, p. 475.

proliferation of the local cells, that in fact inflammation begins from the moment that nutritional derangement occurs. This derangement consists in "the attraction, that is to say, in the direct absorption and the modification, according to circumstances, of large quantities of nutrient substances." In this way the cells of the inflamed organ receive an excessive amount of nourishment at the expense of the fluid parts of the blood. Considering the matter from this point of view, Virchow regards the most characteristic phenomena of inflammation, not as a salutary means of reaction, but as a process distinguished chiefly by its acute nature and especially by the danger that the organism incurs from it.[1]

Samuel and Cohnheim held that inflammation consisted essentially in a molecular lesion of the vascular wall, that the latter, modified by some injurious agency, lost its power of retaining the blood corpuscles, which therefore in consequence of the forces acting upon them were pressed out of the vessels, and then wandered towards the part of least resistance. According to them, inflammation was in nowise a mode by which the organism reacted to extrinsic influences but was merely a primary lesion of the blood-vessels. One experiment of Cohnheim's well illustrates his way of looking at the subject. If by means of a ligature the circulation of the blood in a frog's tongue be stopped for forty-eight hours, and the ligature be then removed, circulation will again proceed, but accompanied with a condition of inflammation, i.e. with the peripheral distribution of the leucocytes, followed by their diapedesis. Cohnheim explains this fact as a direct result of the lesion to the

[1] *Loc. cit.*, p. 399.

vessel-wall, consequent upon its previous prolonged state of anæmia. "I consider that the cause of inflammation," he adds, "should undoubtedly be sought in the vessels themselves; the events outside the vessels appear to be of too subordinate a character to afford an explanation of this phenomenon."[1] And yet very important events must take place outside the vessels. The peripheral tissues, deprived of their nutrition and of their protection by the blood, must become the seat of aggression on the part of the numberless microbes which exist in the buccal cavity. The tissues themselves, or some of them, must at the same time undergo degeneration, which may produce sufficient peripheral excitation to bring about an inflammatory reaction. The instance given by Cohnheim enables us to comprehend his theory without however proving it.

In order to produce what we may call a central vascular lesion independently of the lesion in the other organs situated at the periphery, we may adopt a simple expedient, which consists in introducing the irritating object inside the vessels themselves. In the same work of Cohnheim on embolism, he adduces experiments which were made with the purpose of producing embolic abscesses. To this end he injected into the arteries of frogs a number of substances (such as globules of mercury, powdered cantharides, particles of putrid meat) which might have been expected to cause considerable inflammation, but had no effect at all. Now these substances if introduced under the skin are followed by a marked reaction. If therefore inflammation were only due to a change in the vessel-walls, how is the absence of this change to be explained in

[1] "Die embolischen Processe," 1873, p. 51.

cases where the irritating agent comes in direct contact with the walls themselves ?

Many other facts may be quoted which give the same results as the above experiments of Cohnheim. Pathogenic organisms which readily provoke inflammation are frequently found in the blood without causing any exsudation. In recurrent fever the blood is crowded with spirilla which act directly upon the vessel-wall by their spiral movements as well as in all probability by their toxic products. If Cohnheim's theory were correct, this would cause such an alteration in the walls as to bring about the passage of the corpuscles outside the vessels. Nevertheless no inflammation occurs in the organs during the course of this fever, although the whole body of the patient is 'inflamed' in the highest degree. Many other microbes, such as the anthrax bacillus, cause intense inflammation when inoculated subcutaneously, whereas inflammation in the sense used by Cohnheim does not occur at all, when the same organisms are in the blood. This is again the case when the tubercle bacillus is injected into the blood, while if introduced outside the vessels exsudative inflammation invariably results.

Besides these facts which the theory of the primary lesion of the vascular wall does not take into account the whole comparative pathology of inflammation is an argument against Cohnheim's contention. The reactive phenomena of the invertebrata show that infiltration precedes the vascular events in the evolutional history of the process, and that the leucocytes, led by their sensibility and by means of their amœboid movements, themselves proceed towards the injured spot instead of passively filtering through a vessel-wall.

But even if the theories of Virchow and Cohnheim cannot be accepted in the light of our present knowledge, must we renounce all hope of comprehending imflammatory phenomena, and remain satisfied with a mere description of them as most modern pathologists do?

The study of inflammation from the point of view of comparative pathology proves first of all that this phenomenon is essentially reactive in its nature. The organism, threatened by some injurious agency, protects itself by the means at its disposal. Since, as we have seen, even the lowest organisms, instead of passively submitting to the attacks of morbid agents, struggle against them, why should not the more highly developed organisms, such as man and mammals, act in the same manner? We must conclude then that the invaded organism fights against the injurious cause, but in what way? As the evolution of inflammation shows, it is this phenomenon itself which is both the most general and the most active means of defence among the members of the animal kingdom.

The essential factor in inflammatory reaction is an endeavour on the part of the protoplasm to digest the harmful object. This digestive action, in which the whole or almost the whole organism of the Protozoa takes part, is undertaken by the entire plasmodic mass of the Myxomycetes, while, from the Sponges upwards, it is confined to the mesoderm. In those cases where the victory remains with the invaded organism, the phagocytic cells of this layer assemble, englobe and destroy the injurious agent. This phagocytic reaction, in the lower scale of animal life, is slow, owing to the progression of these cells towards the injurious body

being dependent solely on their amœboid movements ; but as soon as a circulatory or vascular system makes its appearance in the course of evolution, it becomes much more rapid. By means of the blood-current the organism can at any given moment send along to the threatened spot a considerable number of leucocytes to avert the evil. When the circulation is partially carried on by a lacunar system there is nothing to intercept the movement of the leucocytes towards the seat of injury. But when these cells are enclosed within the vessels, they are obliged to adapt themselves specially to fulfil their object, which they do by passing through the vascular wall.

If we accept this conclusion that inflammation in the higher animals is a salutary reaction of the organism and that diapedesis and its accompaniments form part of this reaction, several details of inflammatory phenomena will appear clear to us. For instance the lobed and polymorphous shape of the nucleus of the pus-corpuscles has long been remarked. This particular shape is peculiar to the polynuclear leucocytes, which represent the vast majority (75 per cent.) of the total number of white cells. As it was noticed that a quantity of pus-corpuscles died in the exsudation, this fact became associated with the curious form of the nucleus ; it was said, and is still maintained, that the polynuclear leucocytes are cells predestined to perish and incapable of any considerable activity. On the contrary these leucocytes are precisely the most active cells in the organism. The shape of their nucleus may be more adequately explained as a special adaptation for passing through the vessel-wall. If the process of diapedesis be watched, the difficulty experienced by

the nucleus in getting through will at once be noticed. Directly this has occurred, the rest of the protoplasm follows rapidly. It is obvious that a nucleus divided into several lobes can pass through the wall more easily than one not so separated. Hence in pus the polynuclear leucocytes are more numerous than the mononuclear leucocytes, and hence the lobed shape of the nucleus is found only in the leucocytes adapted for diapedesis and does not occur among the invertebrata (except in a few Cephalopoda).

The facts which demonstrate the untenable position taken up by Cohnheim may be readily explained by means of the theory here set forth. If the irritating agent be outside the vessels, it provokes a typical inflammation, accompanied by diapedesis; if the same agent be within the vessels no diapedesis takes place but the leucocytes fight against the microbes in the blood itself. For instance in recurrent fever, the spirilla undoubtedly act upon the vascular wall without bringing about diapedesis. But the leucocytes increase in number; the leucocytosis is followed by a struggle which is ended by the leucocytes devouring the spirilla. We have here a case of inflammation unaccompanied by diapedesis; the conflict between the phagocytes and the spirilla takes place in the blood itself. Although no diapedesis occurs, there is in recurrent fever great elevation of temperature as well as other symptoms which prove it to be an inflammatory disease. It is apparently a case of inflammation in the blood itself, a sort of 'hemitis' as Piorry considered it might be many years ago. We find the same conditions in animals whose vascular system and general body-cavity are in communication. Thus as we have seen in the disease of Daphnia, caused by the Mono-

spora, the leucocytes often collect in large numbers around the spores of this parasite—their assemblage taking place in the body-cavity.

As another instance we may cite tuberculosis. If inoculated subcutaneously, the tubercle bacilli produce inflammation accompanied by considerable diapedesis. But if the same bacilli be injected direct into the blood, no diapedesis occurs, but the phagocytes will gather round the bacilli within the vessels and form intravascular tubercles. It cannot be said that in the first case (extravascular inoculation) there is inflammation and that in the second (intravascular inoculation) there is none, especially as the same tubercles are formed in both instances. This is another example of an inflammation of the blood itself.

All these cases of intravascular inflammation without diapedesis, as well as the inflammatory phenomena in the young larvæ of Axololotls and Tritons (where it is the migratory cells that collect at the seat of injury), in fact the whole series of reactive phenomena in so many of the invertebrates, prove clearly that *the essential and primary element in typical inflammation consists in a reaction of the phagocytes against a harmful agent.* If the latter be in the general body-cavity, which is filled with blood, the phagocytes will collect here; if in the interior of the vessels, as in recurrent fever or in intravascular tuberculosis, the phagocytes will assemble in the blood itself; if on the contrary the injurious agent is outside the body-cavity or outside the vessels, the phagocytes will emigrate towards the threatened spot—an emigration without diapedesis in the invertebrata and young larvæ of Urodela, or with diapedesis in the vertebrata.

Before phagocytic reaction can take place, these cells

must be excited positively. Negative sensibility may also serve as a means of defence in a mobile organism, such as the plasmodium of the Myxomycetes, which retires from the offending cause. In the cases where the latter has penetrated into the organism, negative sensibility on the part of the phagocytes will leave the field of battle to the parasite, so that, as frequently happens, the death of the organism results. Hence as we rise in the scale, we are met by a progressive evolution of positive sensibility in the leucocytes. In Daphnia the observer is struck by the number of diseases in which phagocytosis is entirely or almost entirely absent. By the time we reach the amphibia, positive chemiotaxis is already very marked and, as Gabritchewsky has shown, it is still more highly developed in rabbits. And yet among the rodents, as in the small laboratory animals generally, there occurs a certain number of rapidly fatal diseases (such as chicken cholera, hog cholera, vibrionian septicæmia of birds), in which phagocytosis is often completely absent. In man and the higher mammals, similar diseases are much less frequent.

But, in addition to the mobile phagocytes adapted by their sensibility to move towards the offending object, there are also fixed phagocytes. A good example of the latter, which are especially developed in the higher vertebrates, is furnished by the endothelial cells of the vessels. Since these cells are contractile and phagocytic, it is natural to conclude that they must also be possessed of sensibility. Thus, if we assume a chemiotactic sensibility of the endothelial cells, we may easily explain the remarkable power of reciprocal attraction possessed by the protoplasmic processes of developing

capillaries, which enables them to meet and form a new vascular loop. We may apply this explanation to account for the fact that in many neoplasms, as in pannus, the vessels penetrate and branch freely in the affected tissue, whereas in the granulomata, such as tubercle, leprosy and actinomycosis, blood-vessels are absent. In the former case there is a positive chemiotactic influence attracting the vascular loops, in the latter a negative chemictaxis or other form of negative sensibility of the endothelial cells. The co-operation of these cells in the inflammatory process would be also directed by their sensibility, at any rate so far as their active contraction is concerned.

There is one more form of sensibility that we must mention, namely that of the nervous system, which aids the phagocytic and vascular mechanisms in their reaction against deleterious agents.

To sum up : *Inflammation generally must be regarded as a phagocytic reaction on the part of the organism against irritants. This reaction is carried out by the mobile phagocytes sometimes alone, sometimes with the aid of the vascular phagocytes or of the nervous system.*

The theory here indicated might be termed the biological or comparative theory of inflammation, since it is founded on a comparative study of the pathological phenomena presented by living cells.

It is above all necessary to emphasise the fact that the essential phenomena of inflammation represent an actual struggle between the phagocytes and the irritant agent. As we have seen that leucocytes are capable of transformation into connective tissue cells, it might be thought that this was the only object for which the accumulation took place. This idea however is nega-

tived by the fact that, in the higher vertebrates, the polynuclear leucocytes do not contribute to the formation of granulation-tissue, although they constitute the large majority of the cells taking part in the inflammation. The mononuclear leucocytes are the only cells, besides the endothelial and connective tissue cells, that are actively engaged in the formation of the new connective tissue. These leucocytes are formed directly from the numerous lymphocytes which flock towards the locality where regeneration is going on.

It has been often thought that the leucocytes which are gathered together in an inflamed area may only serve to effect the absorption of dead cells and microbes, and they have been looked upon as simple 'scavengers' of the organism. We have already seen that this hypothesis is not justified by facts, and that from the very onset of infection the leucocytes wander towards and englobe the parasites in a living condition. In case these direct proofs may not be thought sufficient, I may mention other considerations which tell against this theory.

If the main object of the leucocytic reaction in inflammation were the absorption of solid matters, we should expect to find very pronounced inflammatory phenomena in all cases where a very considerable and rapid absorption is going on. This is however not the case. The metamorphosis of Batrachians is accompanied by an absorption of the larval organs—tail and gills. This is effected very rapidly (in a few days) by the aid of phagocytes which devour all the tissues no longer required by the animal. And yet in this case there are no signs of inflammation, the phagocytes of the tissues in question being quite sufficient by them-

selves to carry out the work of absorption which is evidently a much easier task for them and requires much less activity on their part than does the struggle with parasites.

In mammals the real 'scavengers,' that is to say the phagocytes which carry out the work of absorption, are the macrophages, especially the mononuclear leucocytes. The latter cells play an important part chiefly in the chronic inflammations, such as tuberculosis, while in the acute inflammations it is mainly the microphages, or neutrophile polynuclear leucocytes, that are involved. In erysipelas for example the streptococci are englobed only by the polynuclear leucocytes, and are never taken up by the macrophages, which, however, carry out the entire work of absorption, and even englobe the microphages, many of which perish in the struggle with the microbes and have to be themselves absorbed. If absorption were the only function of the inflammatory emigration, it would be teleologically absurd for this process to end in the formation of pus, i.e. a mass of leucocytes, many of which die and must themselves be absorbed. It is much more natural to assume that the emigration is a reaction on the part of the organism and that in the conflict many of the principal combatants, the microphages, perish on the field of battle. Absorption afterwards ensues and is carried out by another variety of phagocytes.

When I first put forward the biological theory of inflammation eight years ago,[1] I expressed the idea that this reaction is effected by the intermediation of a physiological continuity between "the cells of the connective tissue, those of the endothelial wall and the leucocytes, which form a complete chain and play the

[1] *Biologisches Centralblatt*, 1883, p. 564.

principal part in the inflammation of vertebrates." The connective tissue cells which are first attacked, would, I thought, transmit the action to the vascular wall, the cells of which would contract to facilitate the passage of the white corpuscles. At that time only tactile sensibility of these various cells had been recognised, although certain facts, such as the existence of chemiotaxis, was already suspected from observations of the power possessed by the sexual cells of the Hydromedusæ to travel considerable distances.[1] Since then this chemiotaxis has been definitely proved to exist.

This biological theory has often been considered too vitalistic in its tendency. I need only quote Fränkel's outspoken criticism of my theory from this point of view.[2] "The phagocyte theory presupposes extraordinary powers on the part of the protoplasm of leucocytes, to which are attributed sensations, thoughts and actions, in fact a kind of psychical activity." The sensibility of the phagocytes is not an hypothesis which can be admitted or rejected at will, but an established fact, which cannot be ignored, as it is by Fränkel. Whether they possess powers of thought and volition, as this author accuses me of assuming, is quite beside the question, though we are justified in considering that they possess a germ of these qualities and that their sensibility, like that of various vegetable and animal unicellular organisms represents the lowest stage in the long series of phenomena which culminate in the psychical activities of man.

[1] Weismann, "Die Enstehung der Sexualzellen bei Hydromedusen." Jena, 1883.

[2] "Grundriss der Bakterienkunde." 3rd Ed., Berlin, 1890, p. 203.

As the authorities on these subjects, Herbert Spencer, Romanes and others have shown, psychical phenomena have nothing specific in them, but have developed as an association of the simple actions which we observe in the lower organisms and the cells of different animals.

The accusation of vitalism and animism, which is unjustly cast at the phagocyte theory, might really be more appropriately applied to my opponents, who maintain that the psychical acts of the higher animals are fundamentally different in their nature from the more simple phenomena peculiar to the lower organisms.

It is equally erroneous to attribute a teleological character to the theory that inflammation is a reaction of the organism against injurious agencies. This theory is based on the law of evolution according to which the properties that are useful to the organism survive while those which are harmful are eliminated by natural selection. Those of the lower animals which were possessed of mobile cells to englobe and destroy the enemy, survived, whereas others whose phagocytes did not exercise their function were necessarily destined to perish. In consequence of this natural selection the useful characteristics, including those required for inflammatory reaction, have been established and transmitted, and we need not invoke the assistance of a designed adaptation to a predestined end, as we should from the teleological point of view.

But, it has been urged on several occasions,[1] if the phagocytic reaction has been developed in order to protect the organism from danger, how is it that the phagocytes refuse to act just when the organism is most

[1] For instance by Baumgarten, *Berlin. klin. Wochenschrift*, 1884, and Burdon Sanderson, *Brit. Med. Journ.*, 1891, p. 1085.

threatened? This objection again arises from an insufficient knowledge of the principles of the theory. It is just because the defence by the phagocytes is developed according to the law of natural selection and is not a designed adaptation to a particular end, that cases naturally occur where the phagocytes do not fulfil their functions, a neglect followed by the most serious danger to or death of the organism. In nature the organism is possessed of many characteristics, which may be either useful or injurious to their owner. The former causes the survival, the latter the death of the possessor. Let us take two organisms: one in which the phagocytes are readily repulsed by the microbe, the other whose phagocytes show a positive sensibility causing considerable phagocytosis. The former will soon fall a prey to the parasite and be eliminated by natural selection, whereas the latter will resist the infection, survive and put forth progeny possessed of the same phagocytic properties. Under these conditions the activity of the phagocytes will increase with every successive generation.

But the curative force of nature, the most important element of which is the inflammatory reaction, is not yet perfectly adapted to its object. The frequency of disease and the instances of premature death are a sufficient proof of this. The phagocytic mechanism has not yet reached its highest stage of development and is still undergoing improvement. In too many cases the phagocytes flee before the enemy or destroy the cells of the body to which they belong (as in the scleroses). It is this imperfection in the curative forces of nature which has necessitated the active intervention of man.

The defence of the organism against deleterious agencies, which is at first confined to the phagocytic mechanisms and the somatic system of nerves, by and by spreads to and is undertaken by the psychical nervous apparatus. With the nervous cells which direct the contraction and dilatation of the vessels become associated other cells which control thought and voluntary actions. One function of these psychical cells has been to develop a complete science for the defence of the organism against hostile influences. By its means, methods for assisting the curative inflammation have been devised, as for instance the formation of artificial lesions in order to facilitate the inflammatory reaction. The application of agents which set up inflammation, such as jequirity, the virus of gonorrhea, tuberculin and cantharidin, is the conscious continuation of the defensive measures which have been unconsciously evolved by the long series of animals in their struggle for existence.

But neither the conscious nor the unconscious mechanism is perfect. Medical science should therefore call to its aid all the less complex branches of science, including that of biology, which seeks to investigate organisms and their evolution. Not only inflammation but many other medical problems might be advantageously attacked from the standpoint of comparative pathology. In order to trace the first appearance of febrile reaction, the study of fever should begin with investigations on heat production in the lower animals, continuing on to the vertebrates, such as reptiles, &c. As several of these phenomena have originated at an early geological epoch, the conditions in which the first warm-blooded animals lived should also be taken into account.

Comparative pathology could undoubtedly throw light on the important pathological question of tumours. As many of the lower organisms—both animal and vegetable—are subject to the formation of tumours, the part played by parasites in their etiology could be more easily established and the theory of embryonic aberrations refuted.

The subject of atrophy, intimately connected with that of chronic inflammation, is likewise a suitable one for the application of comparative pathology to its elucidation. Here again the phagocytic phenomena take a prominent part.

If however medical science may learn much from biology, of which it forms but a part, it may at the same time give something in return. General biology may extend its knowledge by including the study of the morbid phenomena of which pathology takes cognisance. In biology difficulties frequently present themselves in the study of the evolutionary processes, because the perfect condition of adaptation in which these phenomena occur in nature, is not a favourable one for analysis. In order to throw light upon the universal law of natural selection, it is necessary to study the less stable phenomena, the less perfect mechanisms, in a word, the phenomena in which the working out of this law can be watched day by day. Now it is just the morbid phenomena with the reactions they provoke, the struggle between the organism and its aggressors, which offer the best opportunity for a consecutive study of the course of natural selection. In this struggle every day some of the combatants, by virtue of natural selection, survive, while others, eliminated by the same means, perish. Now it is the conquering organisms

which survive and the vanquished parasites which become eliminated, now the defeated organisms which are eliminated and the triumphant parasites which survive.

Thus I conclude as I began. General pathology should go hand in hand with zoology or rather with biology, and form one branch of it, that of *comparative pathology*. This science is only in its infancy, and yet it is already in a position to render good service to medicine. By facilitating the analysis of the reactive phenomena, it indicates the elements which should be especially protected and reinforced in the conflict of the organism against its enemies, and thus contributes to the solution of one of the great problems of humanity.

DESCRIPTION OF THE PLATES.

PLATE I.

FIG. 1.—Inflamed spot on the caudal fin of a larva of *Bombinator igneus*, 72 hours after cauterisation with nitrate of silver :—*a*. Phagocytes containing pigment and red corpuscles ; *b*, *c*. Branched cells enclosing fragments of red corpuscles ; *d*. A phagocyte inside a lymphatic vessel.

FIG. 2.—A cyst of the Gregarina of Lumbricus surrounded by a thick and deformed cuticle, and by a follicle formed of connective tissue.

FIG. 3.—A cyst of the same parasite, with only the remains of its cuticle left.

FIG. 4.—A Rhabditis in the midst of a mass of phagocytes. *c*. Thick and deformed cuticle of the parasite.

FIG. 5.—Another Rhabditis, enclosed in the mass of phagocytes of Lumbricus. *c*. Cuticle of the parasite, consisting of several concentric layers.

PLATE II.

FIG. 1.—A cyst of the Gregarina of Lumbricus with its contents divided into cells. The cyst is surrounded by a follicle composed of connective tissue.

FIG. 2.—A mass of phagocytes of Lumbricus surrounding a cyst of Gregarina which they have destroyed.

FIG. 4.—Example of positive chemiotaxis. A plasmodium of *Didymium farinaceum* which has dipped its processes into an infusion of leaves.

FIG. 3.—Example of negative chemiotaxis. The plasmodium of Fig. 4 receding from a 0·1 per cent. solution of quinine.

FIG. 6.—Another plasmodium of *Didymium* repulsed by the hydrochlorate of quinine (0·1 per cent.)

FIG. 5.—The same plasmodium 5 hours after the solution of quinine has been replaced by an infusion of leaves. The negative chemiotaxis of Fig. 6 is converted into positive chemiotaxis.

FIG. 7.—A leucocyte of the salamander. *a.* Attraction sphere (after Flemming).

FIG. 8.—A clasmatocyte from the mesentery of *Triton tæniatus*.

PLATE III.

FIG. 1.—A cyst of Gregarina surrounded by the phagocytes of Lumbricus. (Magnification: objective D and ocular 4 of Zeiss.)

FIG. 2.—Eosinophile leucocyte from man (after Gabritchewsky).

FIG. 3.—One of Ehrlich's cells from a white rat.

FIG. 4.—A giant cell from the spleen of Meriones. *a.* Envelope of the bacillus; *b.* Bacillus of Koch. (The spleen treated with Flemming's fluid and stained by Gram's method and eosine. Magnification: objective 1/18, and ocular 3 of Zeiss.)

FIG. 5.—A giant cell from the spleen of Meriones, containing a calcareous body with a double bacillus. (Stained with hæmatoxylin and Ziehl's fuchsin. Same magnification.)

FIG. 6.—Another giant cell within which the bacillus may be seen surrounded with concentric layers. (Treated and stained as in Fig. 5. Objective 1/18, ocular 2.)

FIG. 7.—A giant cell with a calcareous body containing only a trace of the bacillus *b*. (Fuchsin, hæmatoxylin, 1/18×2.)

FIG. 8.—Another giant cell, in which the bacillus *b* has become converted into a pale rose-coloured body.

FIG. 9.—A giant cell enclosing a fully developed calcareous body.

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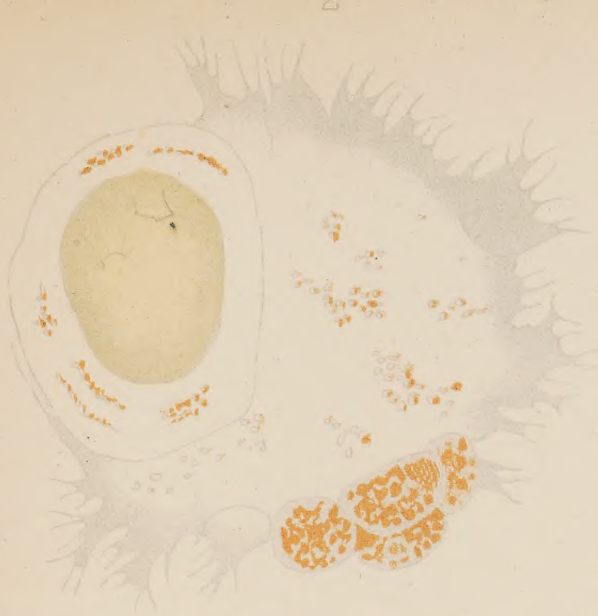

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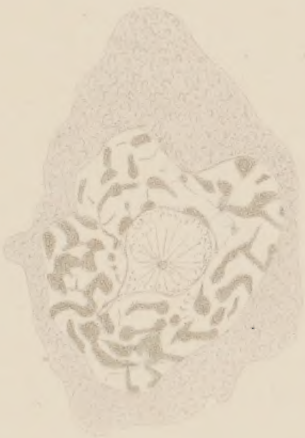

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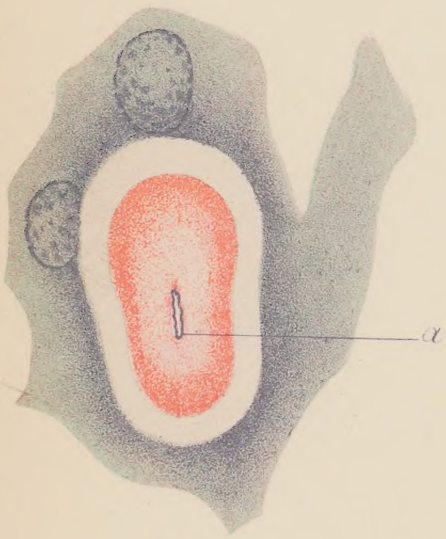

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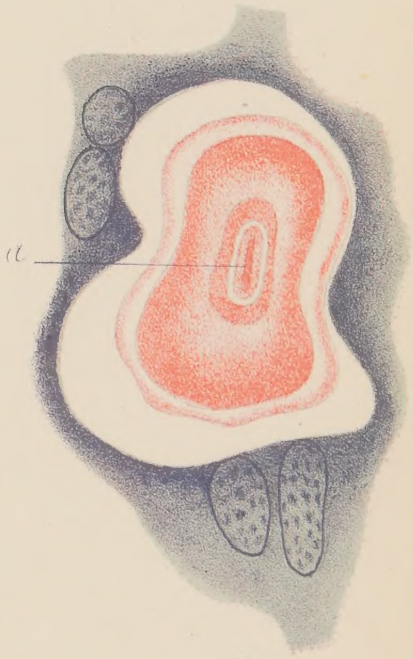

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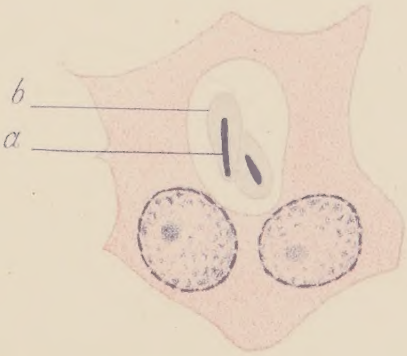

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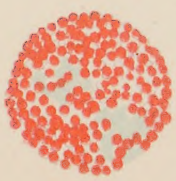

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APPENDIX.

A Consideration of some Criticisms [1] on the Biological Theory of Inflammation.

In the foregoing pages the ontogenetic study of the phenomena of inflammation in the animal kingdom has enabled me to establish a biological theory of this process. I have shown that it really represents an adaptation of the organism to its environment, which has been developed in the course of its never-ceasing struggles against deleterious agencies. "Inflammation generally must be regarded as a phagocytic reaction on the part of the organism against irritants. This reaction is carried out by the mobile phagocytes, sometimes alone, sometimes with the aid of the vascular phagocytes or of the nervous system." (P. 189.)

In analysing the characteristics of inflammation, pathologists have long recognised that the exsudation forms the principal feature, and that the three other classical symptoms, heat, redness and pain, are only of secondary importance. Now the most important constituents of the exsudation are the leucocytes, which are contained in large quantities, not only in purulent but also in serous and fibrinous exsudations. It is rare to find them completely absent in any inflammatory exsudation. The fact, that in the lower animals the inflammatory reaction consists merely in an aggregation of phagocytic cells similar to leucocytes without any accumulation of the body fluids, shows that the existence in higher animals of exsudations free from cells is of secondary importance for our conception of the essential

[1] Podwyssozki. "Memoir in Commemoration of Virchow's Jubilee," Kieff, 1892 (in Russian). Ziegler, "Historisches und Kritisches über die Lehre von der Entzundüng," *Beiträge zur pathologischen Anatomie*, 1892, vol. xii., p. 152, Weigert, *Deutsche medicinische Wochenschrift*, 1893, pp. 17, 37.

nature of the process. It is evident however that these phenomena must be taken into account in formulating any scientific theory of inflammation.

The criticism usually urged against the biological theory of inflammation has been that it totally disregards inflammations in which the exsudation is free from leucocytes. According to Podwyssozki, certain serous inflammations may occur unaccompanied by any phagocytic reaction, and yet we cannot exclude these from the category of true inflammations. He proposes therefore to replace the above definition by the following. "Inflammation is a local reaction, often beneficial, of the living tissues against the irritant substance. This reaction is chiefly produced by a phagocytic activity of the mesodermic cells. In this reaction however may participate not only changes in the vascular system, but also the chemical action of the blood-plasma and tissue-fluids in liquefying and dissolving the irritant agent." This theory has the advantage of including the purely serous inflammations.

In the same way Weigert accuses me of ignoring the existence of exsudations free from cells, and suggests that I do not know what to make of the serous inflammations. Ziegler raises the same objection, although he does not formulate it so precisely. These criticisms however rest upon a misconception which we may remove at once. Although I have devoted a volume to the development of the biological theory of inflammation, I have had to leave many points insufficiently discussed, and it is just to these points that the principal objections have been urged.

The passage of red corpuscles and plasma into the inflammatory exsudations must be looked upon as the result of the activity of the endothelial cells of the vessel walls. (P. 149.) The frequent presence of red corpuscles in the exsudations which are most serous and free from leucocytes shows clearly that in these cases there is a direct passage of the constituents of the blood into the exsudation. If the blood discs are able to pass through the vascular wall, it is evident that the blood plasma must undergo the same fate. It is impossible therefore

to ascribe the serous exsudation to a secretory activity on the part of the endothelial cells. These cells on the contrary must permit of the passage of the plasma and corpuscles in consequence of the contractility which is one of their properties. We may compare this phenomenon to those observed in the Sponges, where the ectodermic cells by their contraction open or close the apertures of the canals and so permit or refuse the passage of fluids with the bodies they may hold in suspension. In both cases, the passage of water through the ectodermic wall in the Sponge, and of plasma through the endothelial wall in inflammation, are brought about in consequence of the sensibility and contractility of the cells concerned. Although the process cannot be called phagocytic in the strict sense of the term, yet its intimate relationship with phagocytic phenomena is very evident.

Phagocytosis is a phenomenon of considerable complexity. When it is exhibited by leucocytes, these cells are in the first place affected by various substances which possess an attraction for them. They proceed towards these substances by means of their amœboid movements and then englobe them. Intracellular digestion may afterwards occur. Here then we have phenomena of sensibility, contraction, ingestion, and production of digestive fluids. As a matter of fact the sequence is frequently broken at some point. Thus when a guinea-pig is infected with anthrax, the leucocytes, acted upon by the bacterial products, approach the microbes; leucocytosis takes place, but phagocytosis is arrested, and the bacteria are either not englobed at all, or to a very slight extent. In this case there is a phagocytic reaction, which however falls short of the mark.

In the most complete phagocytic reaction, all the varieties of phagocytes englobe and destroy the irritant bodies. In other instances it is only the mobile phagocytes which fulfil this function. In a third set of examples, the phagocytic reaction is still less complete. The leucocytes remain in the organs and in the blood and do not pass over into the exsudation; the endothelial cells alone react, but do not accomplish all the phases

of phagocytosis ; they stop short at a stage of contraction which allows the plasma and the red blood corpuscles to pass through the vessel wall. The most familiar examples of this incomplete phagocytic reaction are met with in certain very acute diseases produced experimentally. It is in these cases that purely serous inflammation has been most studied. Thus in the acute diseases produced in guinea-pigs by injection of vibrio Metchnikowii or in rabbits by the coccobacillus of hog cholera when death ensues after a few hours, the phagocytic reaction is limited to this condition of contraction of the vascular endothelial cells, giving rise to a serous exsudation in the infected regions. Where the disease takes a still more rapid course, as in the most malignant forms of chicken cholera in the rabbit, no exsudation at all occurs. There is no phagocytic reaction whatever, but at the same time there is no inflammation.

We see then that serous inflammation is included perfectly well by the general conception of the biological theory without modification. In formulating this theory, I have, in order to make it as short as possible, only mentioned 'phagocytic reaction' in general terms. I have not alluded either to the sensibility or to the contractility of the phagocytes, since these phenomena are already comprised in the one notion of the phagocytic reaction. For the same reason I have not especially referred to the sensibility and contractility of the endothelial cells, which are certainly phagocytic in their nature, although these phenomena play an important part in the production of the serous exsudation.

Since the comparative pathology of inflammation has established the reactive and beneficial character of this phenomenon, we should expect to find certain close affinities between it and other processes of the organism. Thus inflammation is connected by a whole series of intermediate conditions with other phagocytic phenomena, such as the passage of leucocytes through mucous membranes; and chronic inflammation is intimately associated with the atrophy of certain tissues. In fact, from whatever side we may consider inflammation, we shall always find connecting links with other natural phenomena.

Thus from the purely clinical standpoint, no hard and fast boundary line can be drawn between inflammation and hyperæmia, all the intermediate stages between these two conditions being met with at some time or another.

II.

The severest critic of the biological theory of inflammation is Professor Ziegler, who considers that it is quite erroneous to attribute a fundamental importance to phagocytosis in inflammation. I regret that limits of space prevent my reproducing here all his arguments, and must content myself with quoting his principal objections. He writes, "Metchnikoff affirms quite arbitrarily that the pathological phenomenon which interests him represents the essential part of inflammation. He is moreover inconsequent in his statements, for he sometimes regards the phagocytosis exercised by leucocytes and sometimes the accumulation of mesodermic cells as the essential feature." He continues, "I look upon the phagocytosis which occurs in the course of an inflammation as a purely accidental phenomenon, which is often brought about for the simple reason that mobile cells happen to be present, together with a material capable of being ingested by them." (Ziegler, *loc. cit.*, p. 200.)

When we analyse inflammation by means of a study of its ontogeny, we are inevitably forced to the conclusion that phagocytosis is the most primitive phenomenon of the reaction against irritant agents. Inflammation in cold-blooded animals teaches us that increased temperature is not a necessary factor; and the analogous reaction in invertebrates proves that inflammation may occur without any intervention on the part of the blood-vessels. The phenomena thus become more and more simple as we descend the animal scale, till finally the sole phenomenon we have to deal with is phagocytosis. Since the leucocytes are derived from the mesoderm, there is no inconsequence in admitting the existence of a leucocytic phagocytosis and a mesodermal phagocytosis. The facts are so clear that there would be no advantage in dwelling on the matter at any greater length.

Ziegler continues, "When any bodies, such for instance as bacteria giving rise to attracting substances, are present at any spot in the tissues, the leucocytes move towards these bodies, and in some cases manage to englobe them. When on the contrary the foreign bodies, such as bacteria, exercise a repellent or paralysing effect, the cells will move in an opposite direction, or remain where they are. The emigration and phagocytosis then are not brought about by the combative ardour of the cells, but by the properties of the foreign body which has been introduced, or of the tissues and tissue-juices modified by the irritant." He concludes, "The idea that the characteristic feature of inflammation is a struggle of phagocytes must therefore be rejected." (*loc. cit.*, p. 202.)

Ziegler forgets that the attraction and repulsion of leucocytes depend not only on the products of the microbes but also on the sensibility of the leucocytes. Substances which repel the leucocytes of susceptible animals attract on the contrary those of animals which are immune by nature or rendered refractory by vaccination. This fact is so general and well established that no one is justified in ignoring it. It is precisely because on the one side we have microbes which defend themselves or attack by means of their toxic products, and on the other phagocytes which approach and englobe the microbes, that I have formulated the idea of a struggle between two living organisms. None of Ziegler's objections can overthrow this interpretation of the facts just mentioned.

Ziegler proceeds to make use of an argument which has often been brought forward. "In certain cases the phagocytosis exercised by the leucocytes may help to destroy the foreign bodies. In other cases however the phagocytosis may aid in the generalisation of an infectious disease, e.g. when the bacteria can multiply within the cells, as in leprosy, or when they are carried about by the cells." (P. 202.) It cannot be denied that the phagocytic reaction is far from representing a perfect mechanism, as is evidenced by the frequency of many diseases. But there is also no doubt that the generalisation of bacteria takes place much more rapidly in the cases when

they are not englobed by the phagocytes. Thus one often hears that a seat of injury may become infected by tubercle bacilli which have been carried there by leucocytes; but it must not be forgotten that in tuberculosis the leucocytes serve to localise the disease and prevent the dissemination of the bacilli. The importance of the leucocytes as carriers of infective bacilli has been very much exaggerated.

Not approving either of the biological theory of inflammation or of the comparative method on which it is based, Ziegler defines "inflammation as a local tissue-degeneration associated with pathological exsudations from the blood-vessels." (*loc. cit.*, p. 173.) This definition is nothing but a statement of a certain number of the phenomena of inflammation, and does not touch the essential factor in this process. The accumulation of migratory cells in Urodela round irritant bodies, which, as I have shown, takes place without any affection of the vessels, as well as all the analogous phenomena in invertebrata, are quite excluded by Ziegler's definition. And yet any scientific definition should take account of the natural affinities which undoubtedly exist between these phenomena and the inflammation accompanied by a vascular reaction. Another still more striking illustration of the insufficiency of this definition is afforded by tubercle. A tubercle formed within the vessels would not come under Ziegler's definition of inflammation, whereas a tubercle which has developed outside the vessels would be a true inflammation. Now it cannot be denied that intravascular and extravascular tubercle represent essentially one and the same pathological formation. I must conclude then that Ziegler's definition, which leaves the main question untouched and takes no account of natural affinities, must be rejected.

III.

With the exception of the question of serous inflammation, discussed in Section I., Weigert merely makes a few critical remarks with regard to certain subsidiary points in the biological theory of inflammation. My learned critic expresses

doubts as to the justice of comparing the destruction of the microbes within the phagocytes to intracellular digestion. He thinks that there is a contradiction in the fact of intracellular digestion taking place in an acid medium in Protozoa while the processes in the phagocytes are carried out in a neutral or alkaline medium. But besides the case in which the phagocytes show an acid reaction (exsudation-cells of the tail of tadpoles), I may instance the intracellular digestion in multicellular animals. In Actinia this takes place in an acid medium, in the Spongillæ in a neutral or alkaline medium. And yet these two examples are closely allied to each other. It should be premised as a general rule that intracellular digestion may present great variations, and may proceed in media of varying reaction.

Weigert finds another contradiction between my opinion that bacteria are destroyed within the phagocytes and my mention of the ferment of leucocytes, discovered by Leber, which acts outside these cells (a ferment which peptonises gelatin). Here a misunderstanding has arisen. I have never asserted that the phagocytic destruction of bacteria is carried out by means of any ferments, still less by means of those which peptonise gelatin. I have always openly acknowledged that the question as to what substances within the phagocytes harm and destroy the microbes is still quite undecided. They may be ferments, digestive or otherwise, or they may be substances, acid or alkaline, completely different from ferments. We shall have to find new and more perfect methods before being able to solve this delicate problem.

In the question of giant cells, Weigert remains faithful to his old theory, which has been discussed in the "Annales de l'Institut Pasteur," 1888, p. 604. Unfortunately he has not chosen to discuss this subject in his criticism. This is the more to be regretted, since the discovery of the special resistance offered by the giant cells of the Algerian rat to the tubercle bacillus might give rise to an interesting change of opinion. It is unnecessary to insist in greater detail on the fact that this discovery is an important confirmation of my views as to the giant cells being a means of phagocytic defence.

IV.

Having now replied to the principal objections made to the biological theory of inflammation, there is one point of a different nature left to deal with. In spite of his opposition to the phagocytic theory, Ziegler lays a certain claim to priority in this question. I may take this opportunity of replying to this attack as well.

To quote Ziegler's own words: "the phenomenon of phagocytosis has been known for a long time; in the sixth decade of our century, experimental researches on the enclosure of coal-dust and of coloured granules by leucocytes were frequently made, as well as on transport by these cells. In 1874 I observed that, in granulation-tissue, cells having the characteristics of leucocytes with divided nucleus, together with red corpuscles, were englobed and destroyed by large cells. As the result of my researches I concluded that the material englobed was assimilated and that an act of nutrition consequently took place" (p. 197). Ziegler insists upon the fact that "his researches on intracellular digestion in the mesodermic cells were published eight years before the works of Metchnikoff, and that at the time Metchnikoff's first papers on phagocytosis appeared, this phenomenon was well known to pathologists" (p. 199).

Ziegler is astonished that I gave no historical references in my earlier works, and especially in my treatise on inflammation. But in my first paper [1] where mention was made of phagocytes, I quoted "the valuable results of histological and pathological research on the subject of the phenomena of absorption in vertebrates." I referred the reader to Ziegler's text-book of pathological anatomy itself. I did not dwell particularly on Ziegler's work [2] with regard to the ingestion of leucocytes by granulation-cells, for the reason that

[1] *Arbeiten des zool. Inst. zu Wien*, 1883, vol. v. p. 157.

[2] "Experimentelle Untersuch. über die Herkunft der Tuberkelelemente," 1875, p. 68.

this discovery was made four years previously by Bizzozero,[1] who suggested that the leucocytes found in pus in the interior of large cells had been devoured by the latter. Later on Ziegler confirmed this conclusion, but in seeking for the analogies of this process, compared it to the conjugation of cells, such as results in the formation of zygospores in Spirogyra or in that of plasmodia by the fusion of cells, &c. He thus regards the act of ingestion by the leucocytes as a fusion of cells rather than as a preliminary to intracellular digestion.

I need scarcely say that in none of my publications have I laid claim to the discovery of the ingestion of solid bodies by mesodermic cells, nor have I ignored the large number of researches which have been made on this subject. The phagocyte theory however is still the theme of so much debate that I have not had the opportunity of entering fully into historical details. When it is once firmly established, it will be time enough to determine the exact part taken in its foundation by workers such as Panum, Gaule, Roser, &c., who have much more right than Ziegler to be considered the pioneers of this theory.

Ziegler is mistaken in thinking that the ingestion of solid bodies by mesodermic cells necessarily involves the conclusion that the animal organism possesses, in its phagocytic cells, (mesodermic and others) a very important means of defence against pathogenic microbes. In order to establish the fact that the phagocytes constitute an important defensive mechanism, it was necessary to prove that the leucocytes englobe microbes in a living and virulent condition and then injure or destroy them in some way or other. In order to show the importance of the phagocytes, it was necessary to prove that their intervention is of usual occurrence. In this task, I have been obliged to demonstrate the inaccuracy of the work directed against the phagocytic theory and carried out in Ziegler's laboratory. Two of the pupils of this author, Palm[2] and

[1] *Gaz. med. lombarda*, 1871, and *Wien. med. Jahresber.*, 1872, p. 160.

[2] *Beitr. z. path. Anatomie*, vol. ii. p. 480.

Rogowitch,[1] have made some researches on malignant pustule in man and 'charbon symptomatique.' Palm came to the conclusion that in anthrax of man "the cells do not play the slightest part in the sense of the phagocytosis of Metchnikoff." Rogowitch expressed the same opinion as regards 'charbon symptomatique' in several species of animals. And yet it has been definitely shown that both these attacks were based on unreliable data. It is at the present time indubitably proved that the bacilli are englobed in large quantities by the phagocytes both in malignant pustule in man[2] and in 'charbon symptomatique.'[3] The attack emanating from Ziegler's laboratory is thus unjustified by facts.

In this reply to the criticisms on the biological theory of inflammation, I have only considered the more important objections. None of them seem to me to touch either the foundation of the theory or the method upon which it has been built up; hence I do not think that it can be regarded as having been in any way injured by the opposition raised to it.

E. METCHNIKOFF.

[1] *Beitr. z. path. Anatomie*, vol. iv. p. 291.

[2] Karg, *Fortschr. d. Med.* vol. vi. p. 529, and Lubarsch, "Unters. üb. d. Immunität," 1891, pp. 111-114. The latter author summarises his chapter in the following words: "The existence of phagocytosis in human anthrax, as well as its parallelism with the course of the disease and the destruction of the bacilli should be considered as established beyond doubt by the facts I have brought forward." It is inconceivable how Roger (Traité de Médecine de Charcot et Bouchard, vol. i. p. 555) could interpret Lubarsch's article in a directly opposite manner and assert that in the cases quoted by him "there was no connection whatever between the intensity of the phagocytosis and the evolution of the disease."

[3] *Annales de l'Institut Pasteur*, 1889, p. 194. Ruffer, *Brit. Med. Journ.*, May 24, 1890.

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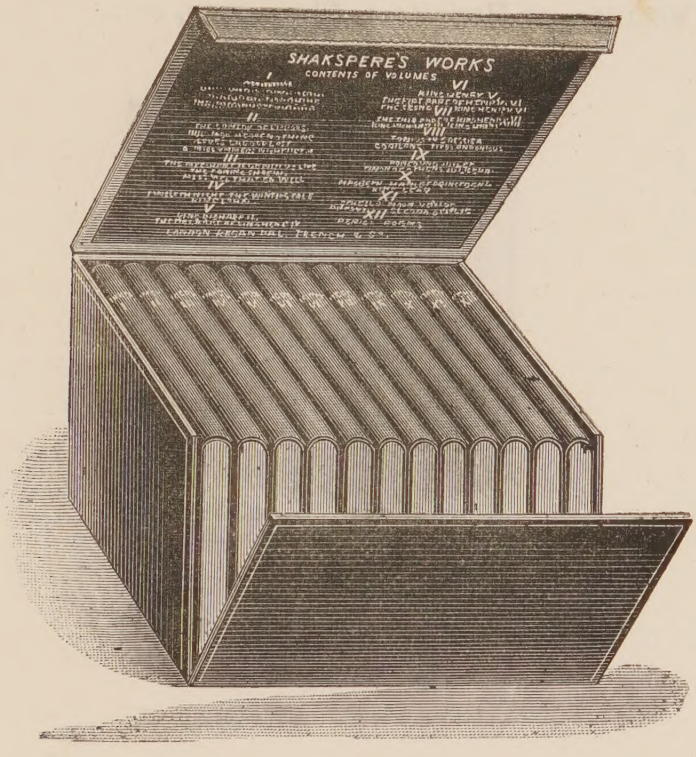

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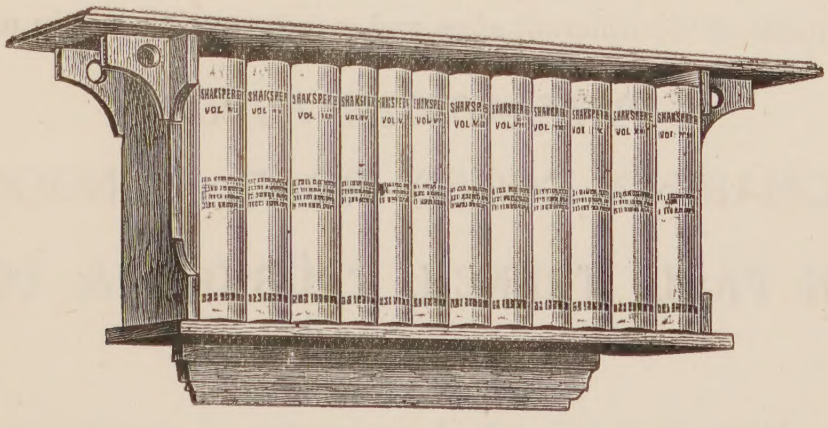

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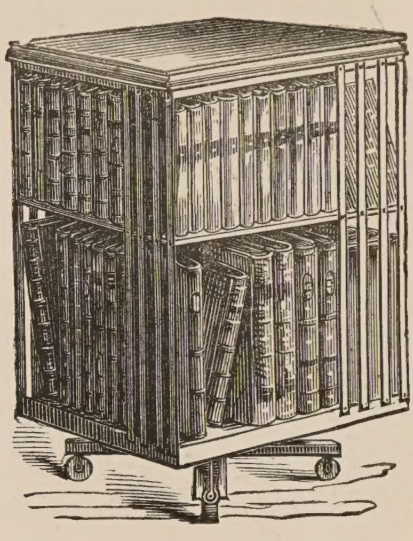

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